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ANNALS OF
INTERNAL MEDICINE

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OBSERVATIONS ON AMEBIASIS IN AMERICAN TROOPS STATIONED IN INDIA *

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AMEBIASIS proved to be a serious problem in American troops stationed in India. Despite the institution of stringent sanitary control measures the incidence of infection with *E. histolytica* remained high and was responsible for a considerable loss of man-power through disability and hospitalization.

The clinical aspects of the disease were of great interest to medical officers. Although most of us had been well indoctrinated in the principles of recognition and control of the disease, few of us were prepared for its protean manifestations and many errors were made until we had become sufficiently conscious of the disease and familiar with its behavior.

Current literature and military directives led us to believe that therapy was a simple matter and that excellent results were to be expected, but experience with symptomatic and parasitologic relapses made it clear that the results of treatment left much to be desired.

The following report is based on observations made on 748 cases of amebiasis. Two hundred and eighteen of these were admitted to the U. S. Army Hospital in Calcutta during the period May 1943 through June 1944. The remaining 530 were admitted to the U. S. Army Hospital at Panagarh from July 1944 to February 1945.

CLINICAL MANIFESTATIONS

Intestinal Amebiasis. This diagnosis was adopted for all cases exhibiting *E. histolytica* in the stools. Since few cases had dysenteric symptoms, the term amebic dysentery was deemed inappropriate. The diagnosis carrier-state, *E. histolytica,* was not used because so many asymptomatic cases, discovered in routine surveys, when questioned carefully gave a history of intermittent diarrhea in the past. Moreover, it implied that the

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parasite was non-pathogenic for the host, a concept open to serious doubt. Of the 748 cases, 735 had intestinal amebiasis. The remaining 13 had hepatic amebiasis without *E. histolytica* in the stools.

In reviewing these cases it was difficult to classify them as asymptomatic, acute and chronic, since there had been no unanimity of opinion regarding the precise meaning of these qualifying terms and since so much depended on the accuracy of the past history. An analysis of 162 cases, in whom a careful and detailed history had been recorded, revealed that 84 per cent had recurrent bouts of diarrhea of varying severity and duration. In most cases these were mild to moderate in severity and of relatively short duration, usually two days to a week. There were no cases of continuous diarrhea over a long period of time. Two per cent of the cases had an acute dysentery of fairly rapid onset with blood and mucus in the stools and tenesmus. The remaining 14 per cent had no gastrointestinal symptoms. Much significance cannot be attached to the relative incidence of these asymptomatic cases, since their number was dependent on the extent to which routine stool surveys were done.

Diarrhea was the outstanding symptom in nearly all cases. Alternation of constipation and diarrhea was common, especially in the more chronic form of the disease.

As a rule the stools were mushy in consistency, bulky, foul-smelling and few in number. Commonly, the first stool occurred immediately after breakfast, was more watery than the others and was associated with urgency. In cases with an acute onset or an acute exacerbation the stools were watery, small in volume and numerous, and were indistinguishable from those seen in bacillary dysentery or acute enteritis. The stools usually contained a moderate amount of mucus but no gross blood or pus. Microscopically, a few red blood cells and an occasional leukocyte could be demonstrated. Gross blood was seen in the more acute forms of the disease. Several cases were admitted because of intermittent rectal bleeding without diarrhea. Their stools contained *E. histolytica,* but no ulcerations could be demonstrated on sigmoidoscopic examination. Since antiamebic therapy appeared to effect a cure, it was assumed that specific ulcers were present higher up.

Pus, usually demonstrable only by microscopic examination, was seen in many of the acute exacerbations and was interpreted as indicating a complicating bacillary infection, even when *Shigella* and *Salmonella* could not be cultured. Administration of sulfaguanidine almost invariably effected prompt, although incomplete, relief of symptoms.

Mild crampy pains, especially in the lower abdomen, were very common. In addition, many patients had vague digestive complaints suggestive of peptic ulcer or gall bladder disease. At times these symptoms dominated the clinical picture, but almost invariably a history of intermittent diarrhea could be obtained.

Slight afternoon elevations of temperature were often noted, but only rarely did they give rise to symptoms. The patients with acute dysentery

had moderate degrees of fever, but when the fever was high it almost invariably indicated a complication—amebic hepatitis, bacillary dysentery or malaria.

Headache, general malaise, lassitude, fatigability, weight loss, and other constitutional symptoms, often attributed to amebic infection,[2] were so common in troops stationed in this area for any length of time, it was our opinion they bore no relation to the disease. Moreover, eradication of the parasite rarely had any effect on these symptoms.

Dr. Krishnan, of the All-India Institute, called our attention to the association of urticaria and amebiasis, which is well recognized in India but which is rarely mentioned in text books[3] or in the literature.[4] We saw a good many patients with urticaria in whom *E. histolytica* were demonstrated. Forty per cent of the urticarias seen in the Calcutta hospital fell into this group.[5] They presented several interesting features. None of the patients gave a history of allergic manifestations in the past or had a familial history of allergy. The rash was usually extensive and was often associated with angioneurotic edema. Diarrhea was a frequent accompanying symptom. Although the rash tended to recur despite intensive epinephrine therapy and dietary restriction, eradication of *E. histolytica* by specific chemotherapy almost always effected complete and permanent cure. Napier[3] is of the opinion that these allergic phenomena are indicative of absorption of allergens through amebic ulcerations. The colonic symptoms were very mild in most cases and completely lacking in others, so that the presence of extensive ulceration was unlikely. Moreover, allergic phenomena were not seen in cases with extensive ulceration of the colon due to other causes, so that it is reasonable to suppose that, when they occurred in amebiasis, they were indicative of sensitization to *E. histolytica* or its by-products, rather than to absorption of allergens from the bowel contents.

Many cases exhibited slight to moderate tenderness and thickening of the colon, especially in the region of the cecum and the sigmoid. The remainder of the physical examination usually revealed nothing of note.

Hepatic Amebiasis. Sixty-nine of our cases had amebiasis of the liver. A detailed analysis of these cases has already been reported elsewhere,[6] so that our findings will be summarized briefly.

The cases fell into the following four groups which had distinctive clinical features:

Acute abscess	7 cases
Acute hepatitis	16 cases
Subacute hepatitis	32 cases
Chronic hepatitis	7 cases

The abscess cases were characterized by liver pain, high fever, leukocytosis and a definite mass in the liver demonstrable either by palpation or by roentgen examination. Cough and abnormal pulmonary findings were common. The acute hepatitis cases were very similar, but no mass could be

demonstrated in the liver, the fever was less marked, pulmonary symptoms and findings were less common and the leukocyte count was lower.

The subacute hepatitis cases had enlarged tender livers, but only half of them complained of liver pain. Fever was inconstant and when present was low grade in character and intermittent. Pulmonary findings and leukocytosis were infrequent. Diarrhea was common and was often the outstanding complaint.

In contrast to the other groups, in which symptoms were usually present for less than 10 days, the chronic hepatitis cases were admitted with liver pain of long duration, ranging from two to 12 months. The symptoms and findings were otherwise similar to those in the subacute hepatitis group.

Pain, the outstanding symptom in all four groups, had a number of distinctive features, which, when carefully analyzed, usually indicated the liver and excluded other structures above and below the diaphragm as its source. These were very important in differential diagnosis. The pain was usually localized beneath the right costal margin or in the right lower chest. It was aching in character, was aggravated by inspiration, cough, change in position and jarring, and frequently radiated to the chest, shoulder, and lumbar region. Compression tenderness of the right lower chest proved to be a very valuable diagnostic sign. Although not considered pathognomonic of hepatic amebiasis, it was an important confirmatory finding and in a few instances made early diagnosis possible in the absence of other signs.

Although only 13 per cent of these cases had a definite history of intestinal amebiasis in the past, 63 per cent had had intermittent diarrhea suggestive of the disease, and 80 per cent were found to have *E. histolytica* in the stools on admission to the hospital.

Early diagnosis, extremely important in prognosis, depended chiefly on a careful analysis of the symptoms and physical findings. Roentgen and laboratory examinations yielded helpful collateral evidence, but were rarely diagnostic. Confirmation usually rested on the prompt specific response to emetine therapy. More direct confirmation requires the demonstration of *E. histolytica* in the liver, which is possible only in the later stages of the disease when an abscess has developed. Even then the parasite may be difficult to find, and it necessitates aspiration of the liver, a procedure not without danger and one found to be unnecessary in early cases.

All cases were treated with emetine alone and 68 of the 69 were cured. The remaining case was greatly improved but failed to meet the rigid criteria of cure laid down. It was our opinion that most cases of hepatic amebiasis could be cured without aspiration if recognized early and treated with sufficient emetine.

Amebic Appendicitis. Amebic ulceration of the cecum frequently gives rise to symptoms suggesting appendicitis.[3, 7] In our experience, pain in the right lower quadrant was common, but a history of intermittent diarrhea and the finding of a slightly tender, thickened cecum without signs of peritoneal irritation, fever or leukocytosis usually suggested the true nature of the dis-

ease, and the demonstration of *E. histolytica* in the stools confirmed it. Emetine and carbarsone therapy usually effected a prompt cure.

We also saw a number of patients with the classical symptoms and physical findings of acute appendicitis who had *E. histolytica* in the stools. At operation the appendix showed inflammation, varying in degree from acute catarrh to acute suppuration with gangrene. On section, a few showed typical amebic ulcerations but many more exhibited motile trophozoites of *E. histolytica* in scrapings from the lumen. At the Panagarh hospital, where all appendices removed at operation were examined for amebae, one-third were found to harbor *E. histolytica.*[8]

These findings raise several interesting questions. Were these all amebic appendicitis or were we dealing with simple acute appendicitis complicating intestinal amebiasis? Were there any distinctive clinical features of amebic appendicitis, and was appendectomy justified in the face of known intestinal amebiasis?

Obviously, those with appendices exhibiting typical ulcerations and trophozoites had amebic appendicitis. It is difficult, however, to assess the rôle of the ameba in producing acute appendicitis in those without ulceration. Although the amebae could have been passive inhabitants from the cecum, the presence of the trophozoite form suggests that the parasite had actually invaded the mucosa. Unfortunately, histologic sections were not available to establish this point. It seems probable, however, that if microscopic amebic ulcerations were present they were not primarily responsible for the acute inflammation, but opened avenues for secondary bacterial infection.

The clinical course and findings in these cases were identical with those in non-amebic acute appendicitis, but a history of amebiasis, intermittent diarrhea or recurrent bouts of right lower quadrant pain suggested the correct diagnosis. In those with active diarrhea, *E. histolytica* were usually found in the stools preoperatively. In others they were demonstrated postoperatively.

Many authorities believe that surgical intervention is contraindicated in intestinal amebiasis with the appendicitis syndrome, unless emetine therapy fails, and that appendectomy may lead to disastrous results.[1] Operation is obviously unnecessary when the symptoms are due to amebic ulceration of the cecum, and it has been amply demonstrated that the post-operative mortality is high when the process is acute.

In our experience, limited largely to mild and moderate intestinal amebiasis, the symptoms referable to the cecum could usually be differentiated from those of acute appendicitis. When the classical signs and symptoms of acute appendicitis were present, however, they usually increased under emetine and carbarsone therapy and appendectomy had to be performed. A surprising number of patients developed acute appendicitis in the hospital while under treatment for intestinal amebiasis. At operation the cecum was often slightly thickened and inflamed, but the appendix was almost invariably the site of acute inflammation and obviously the seat of the trouble.

The post-operative course of our patients was uneventful, and we saw none of the complications seen in cases with acute amebic dysentery which had been mistakenly operated on for appendicitis. All our cases were started on emetine and carbarsone as soon as *E. histolytica* were demonstrated, which may, in part, account for our good results.

Other Forms of Amebiasis. One patient had an amebic ulceration of the skin. He was admitted with mild diarrhea and a painful ulcer of the perianal skin about 2 cm. in diameter. Trophozoites of *E. histolytica* were recovered from scrapings of the base of the ulcer and from the stools. The ulcer had previously been treated with a number of local medications without effect. It healed rapidly under emetine and carbarsone therapy.

Another patient had a most unusual complication—an amebic ulceration of the gall bladder. He was admitted with high fever, pain in the right upper quadrant and diarrhea. On examination he was found to have an enlarged tender liver, leukocytosis and *E. histolytica* in the stools. A diagnosis of acute amebic hepatitis was made and emetine therapy instituted. The following day routine malaria smears were found to be positive for *P. vivax* and quinine therapy was started. Despite this treatment the patient's condition grew worse. Pain and fever increased, the white blood cell count rose and he developed signs of peritoneal irritation over the gall bladder area. A diagnosis of acute cholecystitis or perforating amebic abscess was made and surgical exploration recommended. At operation a large acutely inflamed gall bladder, distended with pus, was removed. The liver was enlarged and engorged, but there was no evidence of abscess. On opening the gall bladder a deep punched-out ulcer was seen in the fundus. Scrapings from the base revealed actively motile trophozoites of *E. histolytica*. Unfortunately, reports on the culture of the pus and the histologic sections are not available. The post-operative course was stormy, but the patient ultimately recovered on emetine therapy. It seems probable that this patient had both acute amebic cholecystitis and acute amebic hepatitis, complicated by malaria.

A number of presumable cured cases of intestinal amebiasis returned to the hospital with a recurrence of diarrhea and cramps. Repeated stool examinations failed to demonstrate *E. histolytica*. Proctoscopic examination disclosed no mucosal changes, and roentgen studies of the colon were negative. A therapeutic trial of emetine, carbarsone and retention enemas of chiniofon cured about 10 per cent of these patients. A few of the patients were apparently cured following a prolonged course of sulfaguanidine in high dosage, but the remainder resisted all therapeutic measures and had to be evacuated to the Zone of the Interior with a diagnosis of "post-amebic colitis."

Rappaport [9] has recently studied a group of resistant chronic diarrheas, which were initiated by amebic or bacillary dysentery, and made the interesting observation that many of them had had allergic manifestations in the past and exhibited sensitivity to food allergens, especially milk, chocolate

and wheat. Removal of these items from the diet resulted in prompt and permanent cure of the diarrhea and cramps. Most of these patients had previously been treated by a variety of methods without relief. After a symptom-free interval of several weeks a tube was introduced into the stomach and, without the patient's knowledge, the offending food was injected. This invariably resulted in a recurrence of symptoms. There seems little doubt, then, that post-amebic colitis is due to the development of food allergy in some instances.

Diagnostic Methods

Stool Examination. Gross inspection of the stools was of little help. Diagnosis depended on the demonstration of *E. histolytica* cysts or trophozoites microscopically. In our experience, the most reliable and rapid technic was the examination of the second, fourth and sixth stools passed after a large saline purge, one ounce of magnesium sulfate crystals in a glass of water. Occasionally patients required a larger dose. The purge was omitted when active diarrhea was present. The stools were collected in pasteboard sputum cups and examined within 15 minutes. A thin saline suspension of each specimen was examined unstained. Whenever possible a fleck of mucus or blood was used in preparing the suspension. In most cases typical actively motile trophozoites of *E. histolytica* were demonstrated in one of the three specimens. When they were not, suspensions stained with dilute iodine solution were examined for cysts. In a few cases concentration methods were employed, but they were time-consuming and rarely demonstrated cysts when the first three direct smears were negative. When the first series of stools failed to reveal cysts or trophozoites, a second purge was administered after an interval of three or four days. It was a curious fact, confirmed repeatedly, that following a purge, trophozoites could not be demonstrated again for several days.

The only cellular elements seen were a few red blood cells and an occasional leukocyte. When the latter were present in any numbers, it was assumed that secondary bacterial infection was present, although pathogenic bacilli were rarely recovered on culture. Charcot-Leyden crystals were extremely rare.

Proctoscopy. Proctoscopic examination was, for a time, carried out in all cases of suspected amebiasis at Panagarh, but was abandoned as a routine procedure because it was time-consuming and added so little information. Not more than one-third of the cases exhibited mucosal changes, and in many these were not sufficiently characteristic to warrant a diagnosis of amebiasis. Direct smears from the mucosa were frequently positive for *E. histolytica,* but only rarely were they positive when the three purged stools were negative. Proctoscopy was useful in excluding other conditions when symptoms resisted specific treatment, and in following the progress of the more chronic forms of the disease with ulceration requiring local therapy.

Roentgen Examination. Barium enemas were done in a number of cases of intestinal amebiasis. Significant changes were rarely found and the procedure was considered of value only in excluding non-amebic lesions when symptoms failed to respond to specific therapy.

Roentgen examination of the lungs and diaphragm was of limited value in the diagnosis of early amebiasis of the liver. The diagnostic changes in the diaphragm [10] occur only in the more advanced stages of the disease and are not seen when the liver is enlarged chiefly anteriorly and inferiorly.[11] Thirty-one per cent of our cases of hepatic amebiasis showed changes in the diaphragm—minor degrees of elevation, flattening and limitation of motion —but only one case had a localized bulge. Thirty-three per cent exhibited pulmonary changes at the right base, chiefly increased markings and haziness, and one case had a slight pleural effusion. These findings often suggested early pneumonia, the one condition most difficult to differentiate from acute amebic hepatitis and abscess, so that the roentgenograms were often misleading.

Roentgen-ray examination of the abdomen was of no value in determining liver size. In a group of 14 cases with easily palpable enlarged tender livers, roentgenograms demonstrated enlargement in only four.

Blood Studies. The white blood cell count was usually normal in intestinal amebiasis. Slight leukocytosis occurred in the acute form of the disease, but when it was much over 10,000 it invariably indicated a complication—usually amebiasis of the liver or bacillary dysentery. The average count in acute amebic abscess of the liver was 15,964 and in acute amebic hepatitis 12,215. Characteristically in these two conditions the relative polymorphonuclear count was only slightly increased. It averaged 83 per cent in the former and 72 per cent in the latter. This point was of considerable aid in differential diagnosis, as first pointed out by Rogers.[12]

Significant eosinophilia was rare, even in those complicated by urticaria. There were no anemias that could be attributed to amebiasis.

The sedimentation rate was elevated in 81 per cent of the cases with hepatic amebiasis and was found to be of great value in following the course of treatment. It remained elevated long after the other signs of activity had subsided and was an indication for further emetine therapy, for, when this was neglected relapse usually occurred. The sedimentation rate was rarely elevated in intestinal amebiasis, although it was noted that following the first few injections of emetine it occasionally rose slightly above normal.

Treatment

The results of treatment are difficult to evaluate in a disease like amebiasis which undergoes spontaneous remissions and in which it is almost impossible to differentiate between relapses and reinfections. It is even more difficult to compare the results of any two investigators since the disease varies so much in different parts of the world, since there are no standard criteria of

cure, and since so much depends on the length of the follow-up period, the skill of the microscopist and the number and technic of stool examinations.

The Rôle of Emetine. When emetine was introduced in the therapy of amebiasis,[13] it was hailed as a specific curative agent. Its dramatic effect in relieving the symptoms of amebic dysentery has been amply confirmed, but experience has indicated it frequently fails to cure.[14] Moreover, serious toxic reactions to the drug have been described. As a result, the rôle of emetine therapy in intestinal amebiasis has undergone a change. Current opinion limits its use to the control of symptoms and favors the newer iodine and arsenic compounds for eradication of the parasite.[14] Some workers have abandoned emetine completely and rely on the iodine compounds alone.[15]

There is good reason to question the wisdom of relegating emetine therapy to the secondary rôle it now plays. The prompt and complete cure of amebiasis of the liver [6] proves beyond doubt that under certain circumstances emetine is capable of eradicating *E. histolytica.* Moreover, remarkably good results have been reported in intestinal amebiasis when large doses of emetine have been employed.[16] No doubt the fear of toxic effects has limited the dose of the drug used and accounts in part for the poor results obtained. It must be conceded, however, that even when large doses of emetine are employed there will be some failures.

The reasons for these failures are worthy of consideration. Since it is the cyst form of *E. histolytica* which persists, it has been suggested that failures are due to emetine's inability to destroy cysts.[17, 18] This explanation is not acceptable. Cysts are non-pathogenic to the host, and there is no evidence that there are free-living trophozoites capable of producing cysts without invading the mucosa. The failure of cysts to disappear from the stools must indicate that emetine has failed to destroy all the trophozoites of *E. histolytica* in the tissues.

Manson-Bahr is of the opinion that the trophozoites become emetine-resistant.[19] This view is supported by in vitro experiments on *E. histolytica* cultures, which, by gradual adaptation to increasing strengths of emetine solution, can be made to thrive in lethal concentrations.[20] Yet, Manson-Bahr's own work on the effectiveness of oral emetine-bismuth-iodide in resistant cases [19] seems to contradict this theory.

The ability of emetine to destroy amebae more thoroughly in the liver than in the intestine may be related to differences in their circulation. In the liver, with its rich blood supply, amebicidal concentrations are readily attained and diffused with safe doses of emetine, but they may not be in chronically ulcerated areas in the intestinal mucosa in which the circulation has been impeded by fibrosis and inflammatory exudate. If this were true, larger doses of emetine ought to be effective. Chopra and Ghosh's work [16] lends support to this view. They found that a high cure rate could be attained with 12 to 15 grains of emetine, but that doses of less than nine grains almost invariably resulted in relapses.

It seems clear, then, that emetine is an effective amebicidal agent, but that

in intestinal amebiasis the dose required for cure may fall into the toxic range. The problem, then, is whether emetine should be supplemented with amebicidal drugs or replaced by them.

Results of Treatment. Circumstances beyond our control made it impossible to conduct any long term experiments, but conditions were such in the Panagarh area that reliable, although admittedly incomplete, data could be gathered on the effectiveness of treatment. The organizations in this area were in fixed installations and had few changes in personnel during the period of this study. Most of them had dispensaries equipped to do stool examinations, and their medical officers were alert to the problem of amebiasis. Patients leaving the hospital following treatment were advised to report any recurrence of gastrointestinal symptoms to their medical officers, and were usually returned promptly for observation and treatment. At some stations routine follow-up stool examinations were done at monthly intervals. This was especially true of food handlers.

This study, based solely on hospital cases, affords fairly accurate data on the symptomatic but not on the parasitologic relapse rate, so that our cure rates are not strictly comparable to those of others who have checked the stools of their subjects routinely over long periods. Nevertheless, this type of study is well suited to a comparison of the results of treatment by various methods in large groups of patients.

Two groups were studied. The first, consisting of 355 successive cases of intestinal amebiasis, was treated in accordance with the principles laid down in a War Department circular on tropical diseases.[21] Asymptomatic cases were given carbarsone, 0.25 gm. three times daily for one week and discharged from the hospital if three normally passed stools were negative for *E. histolytica*. They then took Diodoquin, 0.63 gm. t.i.d., or chiniofon, 0.6 to 1.0 gm. t.i.d., for one week on a duty status. Symptomatic cases were given the same treatment plus enough emetine to control the symptoms, rarely more than four grains. Retention enemas of carbarsone or chiniofon were seldom used except in patients with tenesmus or demonstrable ulcers in the lower colon. The relapse rate on this regime was 9.6 per cent.

In an effort to cut down on the relapse rate, a second group of 162 successive cases was treated by a new regime which included the routine use of a minimum of six grains of emetine, the more extensive use of chiniofon and carbarsone retention enemas and the adoption of more rigid criteria of cure. As a result the relapse rate was lowered to 5.6 per cent.

The basic course of treatment given to all patients, irrespective of symptoms, included injections of emetine, one grain daily for six days, and carbarsone, 0.25 gm. t.i.d., for one week, given concurrently. Following the last injection of emetine a purge was administered and three stools examined as outlined above. If these were negative the patient was discharged from the hospital and given Diodoquin, 0.63 gm. t.i.d., for one week on an ambulatory basis.

If the stools were positive or if symptoms persisted, the patient was

retained in the hospital and given a course of Diodoquin plus nightly retention enemas of 2 per cent chiniofon, usually 5 of 200 c.c. each. Those with symptoms also received additional emetine until they subsided or until a total of 12 grains had been given. At the end of the second week's treatment the stools were reëxamined after a purge. If they were negative for *E. histolytica* the patient was discharged from the hospital and given vioform, 0.25 gm. t.i.d., for one week on an ambulatory basis.

If the stools were positive or if symptoms persisted, the patient was retained and given a course of vioform and five nightly retention enemas of 1 per cent carbarsone in sodium bicarbonate solution. The stools were checked for amebae at the end of the week, and, if negative, the patient was discharged and given another course of oral carbarsone to be taken on an ambulatory status.

Only one patient required a fourth week of treatment before his stools became negative. One hundred thirty-three cases had negative stools at the end of the first week, 24 at the end of the second, and four at the end of the third week.

The following is a tabulation of the treatment employed:

Emetine	
(a) 6 grains	119 cases
(b) 7 to 12 grains	43 cases
Carbarsone	160 cases
Diodoquin	156 cases
Vioform	25 cases
Chiniofon	2 cases
Retention enemas	
(a) chiniofon	30 cases
(b) carbarsone	9 cases

An attempt was made to study the nine relapses that occurred in this group of 162 cases, but the number was too small to demonstrate any significant relationship between relapse and the severity or duration of the disease before treatment or the amount of treatment it took to render the stools negative for *E. histolytica.*

The change in treatment, including the routine use of emetine, apparently effected a reduction in the relapse rate from 9.6 to 5.6 per cent. The significance of this improvement is still open to question, since the average period of observation for the first group was five months and for the second only 2.5 months. Nevertheless, there were other observations that appeared to confirm the impression that the routine use of emetine improved the end results of treatment. Many of the patients in the first group continued to experience gastrointestinal symptoms after treatment, but were not included as relapses, because *E. histolytica* could not be demonstrated in the stools. This was especially true of a large number of patients who had taken repeated courses of carbarsone and Diodoquin on an ambulatory status before coming to the hospital for treatment. Moreover, the only cases requiring evacuation to the Zone of the Interior because of the post-amebic colitis syndrome came from the group which had not received emetine routinely.

Obviously, more long range studies are needed to prove that the routine use of emetine improves the end results of carbarsone and Diodoquin therapy, but there are theoretical reasons for believing that it does, and the present study offers suggestive confirmation.

Hepatic Amebiasis. The dose of emetine required to cure hepatic amebiasis was dependent on the stage of the disease.[6] Acute abscesses required an average of 21.9 grains, acute hepatitis 14.4 grains, subacute hepatitis 11.2 grains and chronic hepatitis 12.4 grains. The largest dose used was 27 grains, the smallest, six grains.

The criteria of cure adopted were: (1) complete absence of pain and fever, (2) absence of liver enlargement, (3) absence of subcostal and compression tenderness, and (4) normal leukocyte count and sedimentation rate.

Treatment consisted of 12 grains of emetine given over a 15 day period, one grain daily intramuscularly, with a three-day rest period after the sixth or ninth dose, depending on the patient's reaction to the drug. Most patients tolerated nine grains well, but a few complained of weakness or exhibited a fall in blood pressure after six grains. Following a three-day rest period, they were able to complete the 12 grain course with no ill effects.

The first course of emetine was followed by a two-week rest period, at the end of which emetine therapy was resumed. Courses of six grains each were then alternated with two-week rest periods until the criteria of cure were met.

The two-week rest period proved to be sufficiently long to prevent the cumulative toxic effects of the drug. In a few of the more acute cases the second and third courses of emetine were given at 8 or 10 day intervals with no untoward effects.

This treatment was supplemented with alternating courses of Diodoquin and carbarsone to eradicate the associated intestinal amebiasis, presumed to be present in all cases. Diodoquin was usually given first to avoid the possible toxic effects of arsenic on the liver, although none was seen in the few cases in which carbarsone was given first.

Toxicity. The cumulative toxic effects of emetine are well known. Among these may be mentioned disorders of the gastrointestinal tract, the cardiovascular system and the neuromuscular system. Their occurrence is dependent on the total dose employed, the route of administration, the duration of rest periods, the preëxistence of cardiovascular or renal disease and individual susceptibility to the drug.

The reports of death following therapy [22, 23, 24] warrant a healthy respect for emetine, but the dangers attending its use have been exaggerated. Armed with a knowledge of the early toxic effects and the necessity for a few simple precautions, the clinician may employ this useful drug in moderate to large doses with safety. Most fatalities have followed the continued administration of large doses of emetine after the early signs of toxicity had appeared.

In our experience with over 500 cases treated with emetine, only one serious complication occurred. In that case, a young nurse with acute

amebic hepatitis, the ward officer failed to follow the treatment schedule outlined above and, as a result, the patient incurred a severe myocarditis, which was still evident both clinically and by electrocardiography one year later.

All patients on emetine were kept at strict bed rest. The blood pressure was determined twice a day and the pulse rate every four hours. The patients were carefully questioned daily about toxic effects, an important precaution, since patients frequently fail to report what to them are insignificant symptoms.

The intramuscular route of administration was used exclusively, because of the reported greater toxicity of the intravenous route.[16, 25] Almost all patients had pain and tenderness at the site of injection, but only rarely were there any signs of local inflammation. The pain presented a number of interesting features. In a few individuals it was noted almost immediately after injection and disappeared in a few hours, but in the others the pain did not appear until a day or two later. Then, in addition to local tenderness, there was poorly localized, constant aching of the injected muscle, or more commonly, of all the surrounding muscles. The aching and tenderness usually lasted for several days to a week after treatment was stopped. Another interesting observation was that when emetine was injected into a number of sites, pain and tenderness did not occur in all of them. Sometimes it was possible to give as many as six injections into the same site with very little pain, while a single injection into the contralateral muscle caused severe pain which lasted for as long as two weeks. Emetine was never discontinued because of pain, but new sites of injection were chosen.

The appearance of mild diarrhea, or a slight increase if it was already present, was fairly common after five or six injections. It usually disappeared during the three-day rest period after the sixth or ninth emetine, and did not recur when emetine injections were resumed. In general, emetine was given in the face of mild diarrhea, but was stopped if it appeared to be increasing or if it was associated with other signs of toxicity.

Occasional patients exhibited a fall in blood pressure, rarely more than 15 or 20 mm. of mercury, which usually occurred between the sixth and ninth doses. This was taken as an indication for a three-day rest period, at the end of which emetine therapy was resumed with no ill effects. If the blood pressure failed to return to normal, which occurred only rarely, emetine therapy was discontinued. In several patients, whose blood pressures were low before treatment and who were debilitated, the daily dose of emetine was reduced to one-half or two-thirds of a grain. In our amebic hepatitis cases, who received the largest total doses, no significant changes in blood pressure were noted late in therapy.

Inconstant tachycardia, rarely more than 90 per minute, occurred in many patients. It did not appear to be regularly associated with changes in blood pressure and was not considered an indication for stopping emetine. In

the patient who developed myocarditis, there was persistent marked tachycardia with extrasystoles.

Unfortunately, electrocardiograms were not available as a routine procedure, so that we have no data on most of these patients. However, we have recently been carrying on a detailed study of emetine toxicity with frequent electrocardiograms, and find that minor myocardial changes are common with the dosage employed in this series, but that they are reversible and quickly return to normal when emetine is discontinued. Furthermore, it appears from this investigation that the rest periods recommended in our high-dose schedule afford an ample margin of safety. Obviously if electrocardiograms are available they should be employed before and during the course of therapy.

With the exception of the case of myocarditis, none of our patients had cardiac complaints, and the physical examination of the heart remained normal throughout treatment.

A few patients on the high-dose schedule complained of generalized weakness which appeared to be unrelated to changes in blood pressure or pulse rate, and which was not associated with demonstrable muscular weakness or other signs of neuritis. When weakness was more than minimal in degree, emetine was discontinued for a few days with prompt return to normal. In our recent work with large doses of emetine, several patients have developed muscle pain and tenderness associated with muscular weakness, especially in the calves, neck and forearms. The symptoms and physical findings were identical with those said to occur in emetine-neuritis,[26] but we were never able to demonstrate reflex changes, sensory disturbances or muscular atrophy. It was our impression that these were examples of emetine-myositis. This problem is being investigated further.

In summary, then, only one serious complication of emetine therapy occurred in over 500 cases. Of the milder toxic manifestations, mild diarrhea, transient tachycardia and a slight fall in blood pressure were fairly common, while generalized weakness occurred occasionally, especially after large doses. The persistence of any of these symptoms for more than one day was an indication for discontinuing emetine therapy, but it could be resumed after an appropriate interval without ill effects.

No significant toxic effects of carbarsone, Diodoquin or vioform were noted. Chiniofon invariably induced diarrhea when the recommended dose of 1.0 gm. t.i.d. was given. Very few patients could tolerate more than 0.8 gm.

Summary

1. Observations on the clinical manifestations and treatment of 748 cases of amebiasis, seen in American troops stationed in India, have been summarized.

2. The outstanding clinical features of intestinal amebiasis were mild to

moderate, intermittent diarrhea, often accompanied by other gastrointestinal symptoms, but rarely associated with any constitutional reaction.

3. Amebiasis was a common cause of urticaria and angioneurotic edema in India.

4. Amebiasis of the liver was a common complication, and varied in severity from an acute abscess to a low grade chronic hepatitis. Emetine alone cured 68 of the 69 cases.

5. The relation of appendicitis to amebiasis was discussed. In some cases appendicitis appeared to be due directly to the ameba, while in others it appeared probable that the ameba had played a secondary rôle in opening avenues for bacterial infection.

6. The simplest and most reliable diagnostic procedure in our experience was the demonstration of the trophozoites of *E. histolytica* in fresh stools passed after a large saline purge.

7. Evidence was presented which suggests that the routine administration of moderate doses of emetine improved the end results of treatment with chiniofon, carbarsone and Diodoquin.

8. Serious toxic reactions were rare, even with large doses of emetine, when the patient was kept at bed rest and observed carefully. Treatment was stopped when the early signs of toxicity appeared, but was resumed after an appropriate rest period.

BIBLIOGRAPHY

1. Strong, R. P.: Stitt's Diagnosis, prevention and treatment of tropical diseases, 1942, The Blakiston Co., Philadelphia.
2. D'Antoni, J. S.: Amebiasis, recent concepts of its prevalence, symptomatology, diagnosis and treatment, Internat. Clin., 1942, I, 100.
3. Napier, L. E.: The principles and practise of tropical medicine, 1943, Thacker, Spink and Co., Ltd., Calcutta, p. 434.
4. Giordano, A. F.: Urticaria and amebiasis, Abstr., Trop. Dis. Bull., 1945, xlii, 37.
5. Cohen, M.: Personal communication.
6. Klatskin, G.: Amebiasis of the liver, Ann. Int. Med., 1946, xxv, 601–631.
7. Sapero, J. J.: Clinical studies in non-dysenteric intestinal amebiasis, Am. Jr. Trop. Med., 1939, xix, 497.
8. Miller, D.: Personal communication.
9. Rappaport, E. M.: Personal communication.
10. Ochsner, A., and De Bakey, M.: Amebic hepatitis and hepatic abscess, Surgery, 1943, xiii, 460.
11. Munk, J.: X-ray appearances in amebic hepatitis, Brit. Jr. Radiol., 1944, xvii, 48.
12. Rogers, L.: Recent advances in tropical medicine, P. Blakiston's Son and Co., 1929, Philadelphia, p. 262.
13. Rogers, L.: The rapid cure of amebic dysentery and hepatitis by hypodermic injections of soluble salts of emetine, Brit. Med. Jr., 1912, i, 1424.
14. Faust, E. C.: Some modern conceptions of amebiasis, Science, 1944, xcix, 69.
15. D'Antoni, J. S.: Further observations on amebic and bacillary colitis in the New Orleans area, Am. Jr. Trop. Med., 1943, xxiii, 237.
16. Chopra, R. N., and Ghosh, B. N.: The therapeutics of emetine, Indian Med. Gaz., 1922, lvii, 248.

17. MANSON-BAHR, P.: Amebic dysentery, facts and fallacies in radical treatment, Abst., Trop. Dis. Bull., 1945, xlii, 207.
18. BTESH, S.: On the treatment of chronic amebiasis, Abst., Trop. Dis. Bull., 1945, xlii, 128.
19. MANSON-BAHR, P.: Amebic dysentery and its effective treatment, Brit. Med. Jr., 1941, ii, 255.
20. HALAWANI, A.: Experimental study of resistance of *Entamoeba histolytica* to emetine hydrochloride in vitro, Ann. Trop. Med., 1930, xxiv, 273.
21. War Department, S. G. O. Circular Letter No. 33, Treatment and control of certain tropical diseases, February 2, 1943.
22. LEIBLY, F. J.: Fatal emetin poisoning due to cumulative action, in amebic dysentery, Am. Jr. Med. Sci., 1930, clxxix, 834.
23. LEVY, R. L., and ROWNTREE, L. G.: On the toxicity of various commercial preparations of emetin hydrochloride, Arch. Int. Med., 1916, xvii, 420.
24. JOHNSON, H. H., and MURPHY, J. A.: The toxic effect of emetine hydrochloride, Mil. Surg., 1917, xl, 58.
25. HEILIG, R., and VISVESWAR, S. K.: On the cardiac effects of emetine, Indian Med. Gaz., 1943, lxxviii, 419.
26. KILGORE, A. R.: Peripheral neuritis following emetin treatment of amebic dysentery, China Med. Jr., 1917, xxxi, 207.

THE MANAGEMENT OF AMEBIASIS *

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THE return of thousands of American troops from remote regions of the world where amebic dysentery is highly endemic makes it imperative that physicians throughout the United States acquaint themselves with the problems that arise in the diagnosis and treatment of this disease. To what proportions this menace might rise is indicated by the statistical reports from the comparatively small India-Burma Theater. Surveys of American troops in the Calcutta area reveal an incidence of amebiasis of 23 per cent.[1] In Myitkyina, Burma, 18.3 per cent of the troops were found to have the parasites in their stools.[2] When it is recalled that at the cessation of hostilities, there were nearly a quarter of a million soldiers in this theater, the number of potentially infested soldiers returning from this one small sector becomes significant.

To aid in this problem, we present some of the experiences in the diagnosis, treatment, and general management of amebiasis, as encountered in a large general hospital in Burma. Owing to the fact that the military situation prevented some of these patients from returning for periodic follow-up examinations and because others were followed for only three to five months, it is apparent that these observations can hardly be presented as a carefully controlled scientific study.

CLINICAL MATERIAL

Three hundred and sixty cases of amebiasis were studied for this report from among those admitted to the 18th General Hospital at Myitkyina, Burma. Most of these patients had been in this area for only a short time, which led us to believe that, in general, we were dealing with infections of relatively short duration. This may account for the mildness of symptoms, the lack of complications, and the generally good response to therapy.

HISTORY AND SYMPTOMS

Of the 360 patients, 140 denied all symptoms even when questioned specifically for them. Table 1 presents graphically the symptoms elicited from the other 220 patients. Twenty-one of these patients have a history of previously proved amebiasis. Only 120 of the symptomatic patients were ill enough to seek admittance to the hospital. The remaining 100 who gave a history of symptoms and the 140 non-symptomatic patients were hospital-

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ized after routine stool examinations revealed the presence of *E. histolytica*. Sixty-eight per cent of the symptomatic patients gave histories of less than one month's duration.

Abdominal pain varied considerably in location and severity. Frequently it was generalized, as found in any type of diarrhea. At other times, it was

TABLE I

Symptoms Elicited in 220 Cases of Amebic Dysentery

Abdominal pain	210	95.4%
Diarrhea	184	83.6
Dyspepsia	112	50.9
Anorexia and malaise	105	47.7
Recent weight loss	51	23.2
Fever	33	15.0
Nausea and vomiting	19	8.6
Bloody stools	12	5.4

localized over some portion of the colon. For example, six cases were admitted as "appendicitis suspects." Another more common syndrome encountered in this group simulated that of peptic ulcer. So protean were the manifestations of amebiasis that any patient with gastrointestinal symptoms became a potential suspect.

Diarrhea varied from intermittent mushy stools to the severe fulminating variety seen in bacillary dysentery. That only 12 patients gave histories of bloody stools is qualified by the fact that the pit type latrine used in this area precluded proper inspection.

PHYSICAL EXAMINATION

The findings on physical examination are summarized in table 2.

TABLE II

Physical Findings in 360 Cases of Amebiasis

Colonic tenderness	225	62.5%
Compression or percussion tenderness over liver	54	15.0
Enlarged tender liver	29	8.1
Enlarged non-tender liver	2	0.6
Liver abscess	1	0.3

Frequently no objective signs whatsoever were found. Only 33 soldiers had fever, but this was at times as high as 104° F. Concurrent bacillary infections in these patients were ruled out by negative stool cultures and dramatic response to anti-amebic therapy. Tenderness over some portion of the colon was a frequent physical finding, not only in the symptomatic but even in the asymptomatic group. At other times, the cecum or sigmoid were spastic and readily palpable. Compression or percussion tenderness over the liver was often present, even when there was no demonstrable hepatic enlargement. Since the majority of these cases were acute and apparently of short duration, weight loss could hardly be expected to be a common finding.

Laboratory Examination

Stool examination is the only laboratory procedure of significance. The technic used is that described in the standard texts.[3, 4] In almost all cases, a saline purgative was administered to produce a liquid stool, which was examined while still fresh.

Of the 360 soldiers in this series, 314 demonstrated trophozoites in their stools, 19 showed cysts, and 27 had both. There appeared to be no correlation between the severity of the disease and the stage of the parasites identified.

In the symptomatic group, 101 patients had rectal cultures taken on admission by the rectal swab technic. Nine of these grew members of the Shigella group. There were no pathogens isolated in the 68 cultures taken in the non-symptomatic group.

Nine hundred and seventy-eight individuals in the Myitkyina area were examined in three stool surveys. One hundred and seventy-eight of these demonstrated *Entameba histolytica,* an incidence of 18.3 per cent. The number of stools examined for each individual varied from one to six, as follows:

Positive on the first stool examination	102	57.3%
Positive on the second stool examination	20	11.2
Positive on the third stool examination	27	15.2
Positive on the fourth stool examination	13	7.3
Positive on the fifth stool examination	11	6.2
Positive on the sixth stool examination	5	2.8

Sigmoidoscopy

Table 3 summarizes the sigmoidoscopic findings in both the symptomatic and non-symptomatic groups.

Table III

Sigmoidoscopic Findings in 229 Cases of Amebiasis

Symptomatic group:	
Number sigmoidoscoped	138
Normal mucosa	94
Mild to moderate changes	28
Severe changes	16
Asymptomatic group:	
Number sigmoidoscoped	91
Normal mucosa	78
Mild to moderate changes	11
Severe changes	2

Various degrees of hyperemia, punctate hemorrhages, or minute erosions were considered mild to moderate mucosal involvement. Severe changes consisted of the usual frank ulcerations seen in subacute and chronic cases.

The diagnosis was established in six cases by identifying the organism from smears made at sigmoidoscopy after repeated stools had been negative.

Treatment

All patients with positive stools, whether they showed cysts or trophozoites or whether or not symptoms were present, received a full course of treatment.

Emetine hydrochloride in doses of one grain daily was administered by deep subcutaneous injection for seven days. At the same time, the patient received 0.25 gm. of carbarsone three times daily for 10 days. If diarrhea was present, he was given a low residue diet. Symptoms were usually controlled by tincture of belladonna, paregoric, or powdered opium, but in severe cases codeine or morphine was occasionally necessary.

While receiving emetine, the patient was confined to bed. If myocardial damage was suspected or if the patient was over 40 years of age, electrocardiograms were taken before and during treatment. Blood pressures were checked twice daily. No electrocardiographic abnormalities were noted during emetine therapy.

On the eighth, ninth and tenth days of treatment, stools were examined for amebae. If they were negative and if the patient was asymptomatic or had only occasional mild symptoms, he was given 0.63 gm. of Diodoquin three times daily for 14 days. At the end of this time, stools were examined again.

After the completion of the emetine and carbarsone, if (1) the stools were still positive, (2) moderate to severe symptoms were still present, or (3) sigmoidoscopic examination still showed abnormal mucosa, the patient received vioform rather than Diodoquin, in doses of 0.25 gm. three times daily for 10 days. At the same time, chiniofon retention enemas were given on alternate days, according to the technic of Manson-Bahr.[5] Occasionally a second course of three doses of emetine was given on the twelfth, thirteenth, and fourteenth days. In some cases in which symptoms persisted, the entire routine was repeated after a suitable rest period of three or four weeks. In general, if the symptoms did not respond to the first complete course of treatment, they did not improve on the second series of carbarsone, emetine and iodine preparations. If treatment failed and the patient could not do full duty, he was returned to the United States for further hospitalization.

On being discharged from the hospital, patients were cautioned to have their stools examined one and three months after concluding treatment.

Toxic manifestations in general were mild and infrequent. The following were attributed to emetine: generalized weakness, generalized muscle aching, diarrhea, nausea and vomiting (31 patients), palpitation and tachycardia (7 patients), foot drop (1 patient), and hematuria (1 patient).

Carbarsone, Diodoquin, and vioform were well tolerated. However, dyspepsia, nausea, vomiting, diarrhea, pruritus ani, furunculosis, and skin rash were encountered frequently enough to suggest that all are potentially toxic. The majority of the patients treated with chiniofon orally developed diarrhea, which at times was so severe that the drug had to be withdrawn.

Pain and local reactions were markedly decreased by injecting emetine by the deep subcutaneous rather than the intramuscular route. Generalized muscle aches seemed decreased when 10 mg. of thiamine chloride daily was included in the routine.

Results

Without any opportunity for long follow-up study, the efficacy of these measures is difficult to evaluate. All but 14 of the 360 soldiers in this series were eventually returned to full duty. In reviewing the case histories of these 14 in whom symptoms persisted despite long treatment, several points become significant. The duration of their symptoms ranged from five to 14 months, in contrast to the great majority whose symptoms were present a month or less. Nine of these patients had had previous episodes of amebic dysentery. Of these, none had had either adequate treatment by present standards or follow-up stool examinations. Eleven had sigmoidoscopic findings which varied from mild hyperemia to frank ulceration.

There were 177 patients available for follow-up study three to five months after treatment. Of these, 84 had been in the symptomatic group. All had negative stools at monthly intervals and at the end of this time, but two still complained of abdominal cramping, three of cramping and occasional loose stools, two of pruritus ani, and one of marked asthenia. Of the 93 patients in the asymptomatic group who were followed for this period, all had negative stools for three to five months, but two who had never before had symptoms now complained of abdominal cramping and loose stools.

Hepatic Involvement

Thirty of the 360 patients were found to have enlargement of the liver at the time of admission, 26 of whom were in the symptomatic group and four of whom were in the non-symptomatic group. Two patients developed hepatomegaly while undergoing emetine therapy, an observation confirmed by at least two medical officers. Twenty-four additional patients had compression or percussion tenderness over the liver area, but did not demonstrate hepatomegaly.

Only one patient demonstrated enough clinical and roentgenological evidence to warrant a diagnosis of liver abscess. Although aspiration was contemplated because of an initially poor response to emetine, the subsequent rapid improvement made this procedure unnecessary. Positive stools were never found in this patient, and he did not have diarrhea.

When the liver was appreciably enlarged and tender, the patient was treated with 1 gm. of chiniofon three times daily for 14 days, rather than with carbarsone which we felt might be toxic. If chiniofon caused excessive diarrhea, vioform was substituted in doses of 0.25 gm. three times daily. Emetine was given in the usual manner except that the patient received a

course of 9 grains. If there was no satisfactory improvement, three more grains were given after a one week interval.

In 20 of the 30 cases with hepatomegaly, the liver promptly receded under this treatment, and tenderness disappeared. In three, the liver was still palpable, although considerably smaller after therapy. These patients were returned to duty because they were clinically well and showed no evidence of liver damage. The remaining seven were returned to the United States because of persistent hepatomegaly and symptoms referable either to the intestine or liver. It is significant that while only 8.6 per cent of the whole group had liver enlargement, 50 per cent of the group of 14 who could not return to duty showed this finding.

It is emphasized that the hepatic enlargement in these cases does not necessarily indicate actual amebic invasion of the liver. Napier has suggested that the entire picture may be caused by hepatic congestion, and that the response to emetine is due to the non-specific effect of the drug on congestion of the liver.[6] Many writers, however, feel that these findings indicate a pre-suppurative stage of liver abscess, or multiple minute abscesses.[7, 8, 9, 10] Whatever the mechanism may be, the dramatic results with emetine make it imperative to recognize hepatic involvement early so that the patient may have the advantage of prompt therapy.

Discussion

The protean manifestations of amebiasis, while pointed out by many writers [4, 5, 6] are emphasized by comparing the clinical findings in this series with those described elsewhere.[11] It seems apparent that such factors as dosage, race of parasite, concurrent bacterial infection, and duration of infection may greatly influence the symptomatology. At times it may be indistinguishable from bacillary dysentery. At other times, diarrhea may be completely lacking.[23]

Physical examination may at times be entirely negative, but tenderness over some portion of the colon is constant enough to direct suspicion toward amebiasis. Compression or percussion tenderness over the liver area may indicate hepatic involvement even when the liver is not appreciably enlarged. It is interesting to observe that two patients who demonstrated that sign later developed hepatic enlargement while under treatment. That liver enlargement in amebiasis may not necessarily indicate actual invasion of the organ by the parasite has been pointed out.

Most laboratory workers in this area and elsewhere [12] agree that the administration of saline purgatives to produce a fluid stool facilitates the identification of trophozoites. For example, it was not a unique experience to identify trophozoites of *E. histolytica* in the fluid stool caused by the purge after vermifuge, where examination of the formed stool prior to treatment had revealed only hookworm ova. Others prefer to use a formed stool with flotation methods [13] and various staining technics to identify the cystic

forms.[14] In our experience, the increase in number of positive stools by using the flotation method was not significant enough to warrant the additional time required to perform the test. All amebae identified were of the small race variety, thought by some to be less pathogenic than the large race.

Special mention should be made of the value of stool surveys in hyperendemic areas to insure prompt diagnosis and treatment. Although there is no absolute evidence to show that all individuals who demonstrate parasites in their stools will develop clinical dysentery, there can be no way of foretelling who will be affected or how severe the clinical course may be. That extensive invasion can occur before symptoms appear is demonstrated by the large number of patients with amebic hepatitis who never have diarrhea and the significant number of asymptomatic patients in this series who demonstrated gross proctoscopic findings. For this reason, the use of surveys for early diagnosis appears desirable. Our experience with surveys suggests that for practical purposes, the examination of three stools for each individual will detect the parasite with an accuracy of approximately 85 per cent.

Sigmoidoscopy appears to be a valuable procedure in the management of amebiasis. In patients with diarrhea who have negative stools, amebae are identified from ulcers seen at sigmoidoscopy frequently enough to make the procedure valuable whenever the etiology is obscure. The appearance of the mucosa and its response to therapy may serve not only as a prognostic aid, but also may help to determine what type of regimen to undertake for further treatment.

The futility of attempting to treat amebic dysentery with any one drug is well recognized. Manson-Bahr has pointed out that hypodermic injections of emetine may not cure amebic dysentery because the drug is not excreted into the feces and does not come in contact with the pre-cystic forms.[15, 16] Clinically, the use of repeated doses of this drug alone has proved a dismal failure.[17] Such a procedure is not only dangerous because of the potential toxicity of the drug, but also because it may result in an emetine-fast strain of amebae. This has been corroborated in the laboratory by subjecting cultures of amebae repeatedly to emetine and then demonstrating its resistance to the drug.[18]

On the other hand, enough failures have been observed in this theater after using oral amebicides alone to suggest that the amount of absorption from the intestinal tract of drugs like carbarsone, Diodoquin, vioform, or chiniofon at times may not be sufficiently adequate to destroy those parasites that have invaded the tissues or the portal system. Emetine still appears to be the most effective drug in these cases. The opinion that no case of amebiasis should be treated with one drug or with even one group of drugs is supported by carefully controlled observations in a British General Hospital, where it was found that neither the iodine nor the arsenical preparations alone were capable of replacing emetine in the treatment of amebiasis.[24]

Although it is acknowledged that emetine is potentially a dangerous drug, the incidence of toxic results when given in small doses with proper

precautions is so low that its use is rarely contraindicated. The oral amebicides with the exception of chiniofon caused but few distressing symptoms, but their potential toxicity has been pointed out.[19]

It has been the feeling in this hospital that the term "carrier" should be avoided. It is true that some writers believe that only a small percentage of individuals who demonstrate parasites in their stools actually have intestinal lesions. Others are convinced that there is always intestinal invasion even though the lesions be only microscopic. The evidence for and against each view is reviewed by Adams.[20] Certainly in our experience, it has been easy to demonstrate potentially destructive trophozoites by administering purgatives to asymptomatic cyst passers. The presence of ulceration in such patients is also evidence that the term carrier is deceptive and misleading. We feel strongly that every individual with *E. histolytica* in his stool has a potentially dangerous condition, whether or not symptoms are present, and should receive prompt and vigorous treatment. This view is advanced by Adams, who writes as follows: "It seems improper to neglect a detected infection until clinical manifestations make their appearance. To do so is to condemn many patients to subsequent unnecessary ill health with the possible development of a major disaster such as an amebic liver abscess. . . . I therefore think they should be regarded as latent cases requiring early treatment." For this reason, we have included emetine in the treatment of *all* patients who have amebae in their stools, whether these be cysts or trophozoites and whether symptoms are present or not.

Sufficient evidence is accumulating to show that bacteria may play a significant rôle in the pathogenesis of amebiasis.[21] To support the experimental evidence that bacteria may enhance the pathogenicity or predispose to invasion is the not infrequent clinical observation that pus cells may be present in the stools of patients with amebic dysentery, even though stool cultures are negative. For this reason, patients in whom symptoms persist after adequate anti-amebic therapy often are benefited by a course of sulfadiazine.

The importance of follow-up stool examinations cannot be too greatly stressed. Too often the criteria for cure have been negative stools after seven to 10 days of treatment. Since it has been shown that cysts seldom appear in the stools until 10 to 20 days after treatment,[22] the patient obviously should be followed for a period of months.

Several factors may determine the prognosis in amebic dysentery. The fact that in this series the parasites were of the small race may account for the relatively mild course most of the patients ran. Two significant findings were present in those patients who could not be returned to duty: (1) The duration of symptoms before diagnosis was made and treatment begun was very long. This clinical observation has been borne out by others,[16] and suggests that the pathogenicity of amebae is enhanced by long existence in the human intestine. (2) Almost all patients of this group received inadequate treatment by present standards. This might suggest that suboptimal doses of amebicides may produce a drug-resistant strain of organism as some-

times occurs in bacterial infections inadequately treated with sulfonamides. Drug-fast strains may also be produced by repeated courses of the same amebicide.

Conclusions

1. The high incidence of amebiasis in American troops in the India-Burma Theater suggests that the disease may become a major health problem in the future.

2. The variation in symptomatology emphasizes that the disease must be considered in the differential diagnosis of any gastrointestinal ailment.

3. Physical examination may be entirely negative, but colonic tenderness should direct suspicion toward intestinal amebiasis and compression or percussion tenderness over the liver toward hepatic involvement.

4. Clinical differentiation of amebic from bacillary dysentery is not always possible. Stool examination by a trained and experienced laboratory technician is the only reliable means of diagnosis.

5. Sigmoidoscopy is sometimes a valuable diagnostic adjunct.

6. The large tender liver frequently observed in amebiasis, although not necessarily signifying a true amebic hepatitis, is frequently associated with the more severe infections.

7. The combined treatment of subcutaneous injections of emetine hydrochloride with oral amebicides is the most satisfactory regimen. The use of either form of treatment alone not only may be unsuccessful, but may actually be harmful by producing a drug-fast strain of parasite.

8. The term "asymptomatic carrier" is dangerous and misleading. It is our opinion that all individuals with amebiasis are diseased and, if treated at all, should be treated vigorously, not only with oral amebicides, but also with injections of emetine, because emetine (a) is the most effective amebicide for parasites that have penetrated the mucosal wall, (b) more effectively eradicates amebae that have penetrated into the portal system without yet producing symptoms, and (c) is comparatively non-toxic when given properly.

9. Sulfadiazine may sometimes be of value in relieving symptoms that persist after adequate anti-amebic therapy.

10. The importance of follow-up stool studies is stressed.

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BIBLIOGRAPHY

1. Blumenthal, H. T., Major, M.C., Commanding Officer, 29th Medical Laboratory: Unpublished Data.
2. Steer, Arthur, Major, M.C., Chief of the Laboratory, 18th General Hospital: Unpublished Data.
3. Stitt, E. R., Clough, P. W., and Clough, M. C.: Practical bacteriology, haematology, and animal parasitology, p. 413, 1942.

4. STRONG, R. P.: Stitt's Diagnosis, prevention, and treatment of tropical disease, p. 501, 510, 1943.
5. MANSON-BAHR, P.: The dysenteric disorders, 1939, p. 196.
6. NAPIER, L. EVARD: The principles and practices of tropical medicine, 1943, p. 444.
7. ROGERS, L.: Amebic liver abscess, Lancet, 1922, i, 463.
8. PALMER, REX E.: Changes in the liver in amebic dysentery with special reference to the origin of amebic abscess, Arch. Path., 1938, xxv, 327.
9. MELENEY, HENRY E.: The pathology of amebiasis, Jr. Am. Med. Assoc., 1934, ciii, 1213.
10. SODEMAN, W. A., and LEWIS, B. O.: Amebic hepatitis, Am. Jr. Trop. Med., 1945, xxv, 35.
11. ROGERS, A. M., and ELSOM, K. A.: Amebiasis as seen in an army general hospital in Assam, Field Med. Bull., USA, IBT, 1945, iv, 316.
12. D'ANTONI, J. S.: Amebic and bacillary colitis in the New Orleans area, Am. Jr. Trop. Med., 1942, xxii, 319.
13. FAUST, E. C., SAWITZ, W., TOBIE, J., ODOM, V., PERES, C., and LINCICOME, D.: Comparative efficiency of various techniques for the diagnosis of protozoa and helminth in feces, Jr. Parasitol., 1939, xxv, 241.
14. PASCHAL, H. W.: A modified rapid staining technique for intestinal parasites, to be published.
15. MANSON-BAHR, P.: Amebic dysentery, Lancet, 1944, ii, 718.
16. MANSON-BAHR, P.: Treatment of amebic dysentery, British Med. Jr., 1941, ii, 255.
17. LEISHMAN, A. W. D.: A year of military medicine in India, Lancet, 1944, ii, 231.
18. BARRIN, H., and ARITAS, R.: Compt. rend. Soc. d. biol., cxxx, 495, quoted from 15.
19. DAVID, N. A.: Uncontrolled use of oral amebicides, Jr. Am. Med. Assoc., 1945, cxxix, 572.
20. ADAMS, A. R. D.: Amebiasis with special reference to treatment, Trans. Roy. Soc. Trop. Med. and Hyg., 1945, xxxviii, 237.
21. NAUSS, R. W., and RAPPAPORT, I.: Studies in amebiasis: I. Pathogenesis of mucosal penetration, Am. Jr. Trop. Med., 1940, xxvi, 107.
22. PAYNE, A. M. M.: Amebic dysentery in Eastern India, Lancet, 1945, i, 206.
23. SAPERO, J. J.: Clinical studies in non-dysenteric intestinal amebiasis, Am. Jr. Trop. Med., 1939, xix, 497.
24. LOWE, J., Professor of Tropical Medicine, School of Tropical Medicine, Calcutta: Personal Communication.

ACUTE PERICARDITIS: A STUDY OF EIGHTEEN CASES AMONG SERVICE PERSONNEL *

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Pericarditis in itself may be serious or unimportant, or it may be merely an incident in other serious and often fatal diseases. It is often masked by the underlying illness and not thought of until discovered in the course of a physical or roentgenologic examination.

Acute pericardial disease may be classified into three main types: acute fibrinous, acute serofibrinous and purulent. Acute rheumatic fever is the most common etiologic factor in the production of the fibrinous and serofibrinous types. In this condition the pericarditis is a part of a pancarditis in which the endocardium and the myocardium are also affected.[1] Other etiologic factors in the production of these same types are influenza,[2] pneumococcic pneumonia, primary atypical pneumonia [3] and tularemia.[4] Purulent pericarditis is a complication of disease produced elsewhere in the body by pyogenic bacteria and initiated by hematogenous spread or by direct extension. Besides the etiologic factors already mentioned acute myocardial infarction, penetrating wounds of the thorax, uremia, malignant tumors, lupus erythematosus, periarteritis nodosa and undulant fever should be listed. It may follow tonsillectomy and has been reported following operative procedures, including thyroidectomy.[5] It has been observed in epidemic form.[6]

It has been said that the diagnosis of acute pericarditis is more often missed than made. Smith and Willius [7, 8, 9] found 373 cases of pericarditis in the course of 8,912 necropsies, an incidence of 4.3 per cent; in 58 per cent of these 373 cases acute pericardial disease was present.

Diagnosis

In the diagnosis of pericarditis, the general symptoms are those of any severe infectious illness. The local symptoms and signs are few but are characteristic when present. Pain, if present, is sharp, intermittent or continuous, and is usually referred to the precordium and left shoulder. It is accentuated by bodily movements, cough and inspiration. The accentuation of pain under these circumstances is helpful in the differential diagnosis from myocardial infarction according to Wolff.[6]

Cough, orthopnea, hoarseness and dysphagia or dyspnea, weakness, faintness and venous congestion may be produced when pericardial effusion

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develops rapidly and causes pressure on the lungs and trachea or cardiac tamponade.

A to-and-fro pericardial friction rub which may be heard within one to a few hours after the onset of pain, when it is present, is diagnostic of pericarditis. It may be loud and is most frequently heard along the left border of the sternum. Willius [10] stated that a rub is heard in less than 20 per cent of cases in which the pericardium is known to have been involved. Many cases of acute pericarditis will be overlooked if the development of this phenomenon is awaited.

The earliest sign of pericardial effusion is found on roentgenologic examination. It consists of a bulging of the heart shadow, just above the cardiodiaphragmatic angles. As the serous exudate increases, the cardiac contour is rounded out, and with the patient standing, it may resemble a water bottle. The size of the heart is difficult to determine because the shadow is usually buried in the shadow of the pericardial effusion. The water bottle configuration is not conclusive evidence of pericardial effusion because the same configuration may be produced by acute cardiac dilatation.[11] According to Freedman [12] roentgenologic examination is most reliable when it is repeated daily. Any considerable change in the size of the shadow within a short period of time is the best sign of pericardial fluid. As the fluid increases to the point of cardiac tamponade, the contour of the heart shadow approaches that of a "water bottle" flask and the right and left sides appear symmetrical.

Compression of the right auricle and great veins by the fluid in the pericardium may result in high venous pressure and give rise to enlargement of the liver and tenderness on pressure. The progressive blocking of the hepatic veins and inferior vena cava may give rise to ascites with or without edema of the legs. With large pericardial effusions, the minute volume of blood entering the heart and being pumped into the circulation gradually decreases. This decrease results in low blood and pulse pressure, faint heart sounds, tachycardia and paradoxical pulse.

Electrocardiograms are of distinct diagnostic value in pericarditis. The sequence of changes is best illustrated by serial tracings. A tracing suggestive of chronic tuberculous pericarditis may lead one to secure other confirmatory evidence. In acute pericarditis (figure 1*A*) the most characteristic picture is elevation of the RS–T segment in all three standard leads or in Leads I and II, in Leads II and III, or in Lead I alone. In the early stage the T-waves may be exaggerated and rather sharp, or they may have a dome-shaped summit. The early changes may subside rapidly. In the subacute stage of pericarditis the elevations disappear and the T-waves may be negative (figure 1*B*). The changes of chronic tuberculous pericarditis are chiefly those observed in chronic constrictive pericarditis (figure 1*C*) and include low voltage of the QRS complexes in all the standard leads and low voltage or inversion of the T-waves in all standard leads.[13]

FIG. 1. Electrocardiograms. *A*. Acute pericarditis in case 1. Elevation of RS-T segment in Leads I, II and IV may be noted. *B*. Subacute pericarditis in case 2; the T-waves are of low voltage or negative. *C*. Chronic pericarditis in case 3. Low voltage is noticeable through all leads.

To make the correct diagnosis of pericarditis requires all information that can be obtained by examination of the heart and chest, a complete study of the circulation, radiologic examination, fluoroscopy, electrocardiography and perhaps paracentesis.

In the course of an infection or during a postoperative convalescence, the sudden onset of dyspnea, pain in the thorax with a rapid weak pulse, a drop in blood pressure, chills and fever, and a grayish pallor should suggest pericarditis.

Series of Eighteen Cases

This paper is based on 18 cases of acute pericarditis which were observed in 17 months on a cardiorespiratory service at a United States Naval Hospital.

Eight of the patients were 18 or 19 years of age, eight were in the third decade of life and two in the fourth. All were males; one (case 18) was a Negro (table 1).

Table I

The Etiologic Factors, Results and Sick Days in Series of Eighteen Cases

Case	Age, yrs.	Etiologic factor	Result	Sick days
1	18	Rheumatic fever	Died	6
2	21	Bronchopneumonia	Died	28
3	18	Tuberculosis	Transferred	211
4	34	Nonspecific	Duty	100
5	35	Bronchopneumonia	Discharge	172
6	23	Rheumatic fever	Hospital	73
7	21	Nonspecific	Duty	152
8	18	Pharyngitis, rheumatic fever	Hospital	137
9	25	Tracheobronchitis, septicemia	Hospital	287
10	20	Lobar pneumonia, left pleural effusion	Transferred	271
11	18	Atypical pneumonia, right pleural effusion	Hospital	88
12	23	Pharyngitis	Discharge	155
13	18	Pharyngitis	Hospital	185
14	22	Tuberculosis	Hospital	76
15	19	Pharyngitis	Hospital	36
16	18	Rheumatic fever	Died	10
17	19	Rheumatic fever	Transferred	280
18	22	Lobar pneumonia	Died	1

Acute pericardial disease is seen almost exclusively in younger individuals. For that reason, many cases are seen in military service where the majority of personnel are within the age group in which infectious diseases are prevalent.

Various etiologic factors were responsible for the pericarditis in this series (table 1). Rheumatic fever was considered the cause in five cases; pharyngitis in three, pneumonia in five, septicemia in one, tuberculosis in two and in two a nonspecific type of pericarditis was present. These factors are the same as those which have been previously noted in textbooks and reports, but the incidence varied somewhat.

When pericarditis resulted from an infectious disease, the patient was usually seriously ill before the pericarditis developed; it usually developed in from three days to two weeks after the onset of the infection. At times the exact primary infection was difficult to determine. Present symptoms or a past history of symptoms referable to either the joints or the heart were considered to be definitely rheumatic. Episodes of acute pharyngitis, particularly when associated with constitutional reactions of fever and malaise were considered significant. Pneumonia, tuberculosis and septicemia were diagnosed by clinical and laboratory examinations. Two patients did not give a history of any recent infectious process, and their condition was classified as a nonspecific inflammatory pericarditis which is reported as occurring under various circumstances unassociated with the commonly recognized causative factors.

A rub was heard during some stage of the illness in 14 of the 18 patients in this series.

In this group of 18 cases two men were cured (table 1). (The term "cured" is used in a restricted sense to mean "had no symptoms or signs present from three to five months after the onset of their illness.") Two were discharged from the service after six months in the hospital, because of residual changes. Ten continued to receive hospitalization because of recent onset, or the presence of valvular heart disease, empyema or effusion under treatment. One of these (case 3) is known to have died after being transferred to another hospital. Four men died in the hospital, two from pneumonia and purulent pericarditis, and two from rheumatic pancarditis with pericarditis. Both of the latter had had a previous attack of rheumatic heart disease not diagnosed clinically. The sick days of these 18 men had varied from one to 287 at the time of writing this paper.

Three representative cases are reported in detail.

Case Reports

Case 1. A sailor, aged 18 years, was admitted to the hospital because of swelling and severe pain in his joints of three days' duration and pain in his left thorax for one day. He had been told that he had rheumatic fever five months previously. At that time he had been playing football and noted pain in both legs which was not disabling and did not require medical treatment. Thereafter he had felt well until his present illness. The articular pain began in his right elbow and was associated with swelling. After two days, the pain and swelling spread and involved his left wrist. The day before admission his knees and ankles were so painful that he was unable to walk. Concurrently a sharp, almost continuous pain developed over his heart. This pain was worse on inspiration so that he breathed with difficulty.

The patient weighed 197 pounds (89.4 kg.) and was well developed. He appeared acutely and seriously ill. His temperature was 100° F.; the pulse rate was 132 beats per minute and blood pressure was 90 mm. Hg systolic and 70 mm. diastolic. The respiratory rate was 28 per minute and breathing was shallow and labored. Fine crackling râles were heard at the bases of both lungs. Palpation revealed friction fremitus over the precordium, and a loud grating pericardial friction rub was heard in that region. The heart was enlarged to the right and left. Both systolic and diastolic murmurs were heard in the region of the mitral valve. Tenderness was

noted in the upper part of the abdomen. His ankles, knees and left wrist were red and swollen and so painful that light pressure on these parts caused him to cry out.

Laboratory data on, or shortly after, admission included a negative blood culture and a negative Kahn reaction on the blood. The value for hemoglobin was 71 per cent; erythrocytes numbered 3,310,000 per cubic millimeter with an occasional nucleated cell, and leukocytes numbered 5,850 per cubic millimeter. The differential count revealed polymorphonuclear cells 95 per cent, lymphocytes 4 per cent and monocytes 1 per cent. The value of blood chlorides in milligrams per 100 c.c. was 360, and of serum proteins in grams per 100 c.c. 6.8. A bedside roentgenogram of the chest revealed a hazy mottled increase in density in the lower part of both lungs (figure 2). The transverse diameter of the heart was 19.6 cm. and of the chest 31.5 cm. Because the roentgenogram was made at the bedside, the size of the heart could not be accurately determined, but it took up more than 50 per cent of the transverse diameter of the chest and was enlarged to the right and left. An electrocardiogram revealed upward displacement of the RS–T segments in Leads I, II and IV. The T-wave in Lead III was inverted (figure 1*A*).

A diagnosis of rheumatic heart disease with pericarditis was made.

The patient was placed in an oxygen tent and given sedatives and large doses of sodium salicylate. On the second day in the hospital his temperature rose to 103.2° F., and the pulse rate continued to be rapid. Respirations were shallow and labored, and he continued to have pain in the left side of the chest. There was no change in the

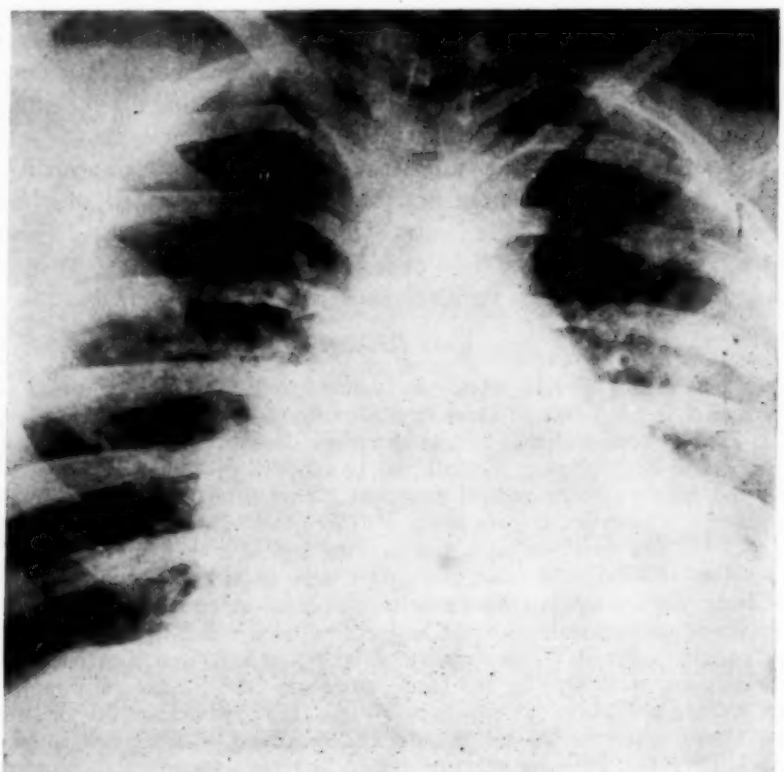

FIG. 2 (case 1). Heart is enlarged to the right and left. Contour of the heart should be noted.

intensity of the pericardial rub. Sulfadiazine was administered in adequate doses, and on the third day in the hospital the temperature became normal. However, dyspnea continued and the patient was slightly confused. The liver became palpable and tender. There was no change in the heart. Digitalization with cedilanid was carried out rapidly, and administration of this drug was continued parenterally.

On the fourth day in the hospital the patient exhibited a grayish pallor. Temperature was 101° F. Signs of congestion in both lungs increased, but the condition of the heart and the pericardial rub continued as before. Administration of penicillin in adequate dosage was begun, but the temperature continued to rise and was 102.6° F. on the fifth day. The patient became more dyspneic and the temperature continued to rise. He did not respond to treatment and died.

Postmortem examination revealed rheumatic pancarditis with acute fibrinous pericarditis. The heart was dilated and hypertrophied and covered with a yellow-gray shaggy fibrinous exudate. On opening the heart the mitral valve was thickened and the adjacent edges of the leaflets fused. The free border was rolled and studded with verrucous vegetations. Fine granular vegetations were seen on the cusps of the aortic valve. The attached chordae tendineae were thickened. The myocardium showed small foci of infiltration and an occasional Aschoff cell. There was no fibrosis. A small amount of fluid was found in each pleural cavity. There was passive congestion of the liver.

Acute pericardial disease as a complication of rheumatic fever may subside spontaneously. However, Holt [14] reported on the gravity of pericarditis in rheumatic fever. Acute pericarditis was the turning point in the disease for 26 of her patients, only one of whom was known to be alive three years after the attack. In our experience, pericarditis may be a concurrent sign and symptom of a rheumatic pancarditis.

Case 2. The patient, aged 21 years, was admitted to the hospital because of pain in the left side of the thorax. He had had pneumonia at the age of one year and sinus trouble for about four years. A severe attack of the latter had occurred one year before admission, and irrigation of the sinuses was performed about one week before. Otherwise, his general health had been good until the onset of his present illness. Five days prior to admission he first noticed malaise and anorexia and experienced nausea and vomiting on two occasions when he attempted to eat. Two days before admission he had epistaxis. The same day he had a shaking chill followed by fever and pain in the left side of the chest, and he coughed up some yellow sputum. The pain was aggravated by respiration.

On examination dyspnea and cyanosis of the fingernails were noted. The patient was restless, apprehensive, and appeared seriously ill. The temperature was 102.8° F.; the pulse rate was 120 beats per minute and blood pressure was 112 mm. Hg systolic and 60 mm. diastolic. Respiratory rate was 32 per minute and respiration was shallow and labored, but there was equal movement on both sides. The mouth was dry. The heart was enlarged to the right and left. There were no murmurs. On percussion there was dullness in the base of the left lung and tubular breathing; crackling râles were heard in the same region.

A trace of albuminuria was found. Gram stain of the sputum revealed many gram-positive cocci in clusters and pairs. The value for hemoglobin was 84 per cent, the erythrocyte count was 3,940,000 per cubic millimeter, and the leukocyte count, 12,050. The differential count revealed polymorphonuclear cells 76 per cent, lymphocytes 21 per cent, and monocytes 3 per cent. In the bedside roentgenogram of the chest (figure 3*A*) the transverse diameter of the heart was 20.8 cm. and that of the chest was 29.5 cm.

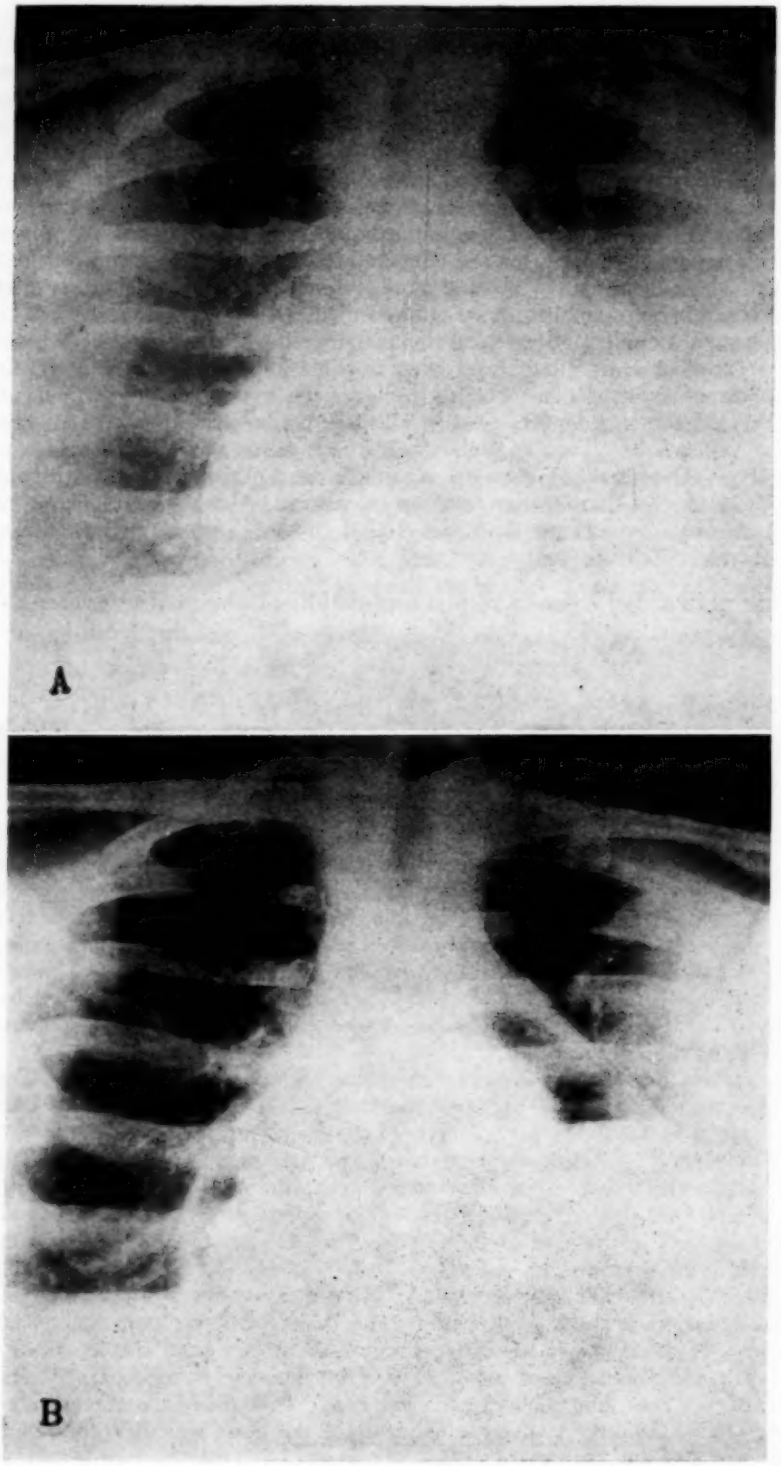

FIG. 3 (case 2). *A*. Heart is enlarged to the left and right. *B*. Actual size of the heart is indicated. View made after withdrawal of fluid from and injection of air into the pericardial sac.

A diagnosis of bronchopneumonia with pericarditis was made.

The patient was placed in an oxygen tent and given sedatives. Intravenous administration of penicillin was begun at once with 100,000 Oxford units in 5 per cent solution of glucose and thereafter 15,000 units were given every three hours. Also 1 gm. of sulfadiazine and 10 grains (0.65 gm.) of sodium bicarbonate were prescribed every four hours. By the third day in the hospital the patient's color was improved. The liver was enlarged about three fingers' breadth below the right costal margin and was tender. Crackling râles were still present in the left lung.

The following day the pulse became weak and the rate rose to 120 beats per minute. The heart tones were distant and muffled. On the fifth day in the hospital the patient was restless and dyspneic. The pulse was paradoxical. Pericardial paracentesis was done and 90 c.c. of cloudy yellow fluid with coagulum were aspirated. The temperature became normal that day.

The next day the patient again was dyspneic and uncomfortable. He could not eat and could drink little. The paradoxical pulse was weak. Blood pressure was 100 mm. Hg systolic and 60 mm. diastolic. The temperature was 101° F. The patient breathed more easily after 450 c.c. of cloudy yellow fluid were removed and 20,000 Oxford units of penicillin were instilled into the pericardial cavity. The blood pressure rose to 140 mm. Hg systolic and 90 mm. diastolic; the pulse became stronger and was no longer paradoxical. Examination of the purulent fluid, including a smear for tubercle bacilli, revealed no organisms, and the culture was negative. A guinea pig was inoculated with the fluid with negative results. Studies made on other occasions were also negative, and the differential cell counts made revealed from 79 to 96 per cent polymorphonuclear leukocytes.

The patient's abdomen became tender and distended. The administration of sulfadiazine was discontinued, and local application of heat, enemas and intramuscular injections of methylsulfate (prostigmine) were given with little relief. Profuse diaphoresis, precordial pain and dyspnea were present. Dullness and a pleural friction rub were noted in the base of the left lung. On the seventh day in the hospital 370 c.c. of cloudy yellow fluid with a bloody pellicle were removed from the pericardial cavity, and 35,000 Oxford units of penicillin were instilled into it. A harsh grating pericardial friction rub was heard. The pericardial shadow was slightly decreased on roentgenologic examination. The temperature continued to be elevated and the record was of a spiking nature, especially in the evening. Adequate fluids were given orally and intravenously. Oxygen was used as needed. Respiration seemed less labored.

On the ninth day in the hospital dyspnea and restlessness were noticeable. At this time 585 c.c. of clear yellow fluid were withdrawn, and 100,000 Oxford units of penicillin and 150 c.c. of air were injected into the pericardial cavity.

Another bedside roentgenogram (figure 3*B*) following instillation of air into the pericardial sac revealed a greatly thickened pericardium, a large amount of fibrinous exudate which partially obscured the border of the heart and evidence of pneumonitis in the left lower lobe. The patient seemed improved and did not complain of shortness of breath. He was coughing a little and râles were heard in both sides of his chest. He continued to have fever as high as 102° F. Two successive blood cultures were negative.

On the fourteenth day in the hospital the patient complained of pain in the right side of the chest and a pleural friction rub was heard in that area. He again noted some shortness of breath for which he requested oxygen. The pericardial rub, previously heard, disappeared. Removal of 375 c.c. of yellow fluid made a total of 1,870 c.c. removed from the pericardial cavity, and 100,000 Oxford units of penicillin and 250 c.c. of air were instilled into the pericardial sac. The temperature had slightly decreased to 101° F. An electrocardiogram revealed low voltage of the

T-wave in Lead I and inversion of the T-waves in Leads II, III and IV. These findings were suggestive of subacute pericarditis (figure 1*B*). The patient again seemed improved and took an interest in things about him. Oxygen therapy was discontinued. He continued to have upper abdominal soreness; his temperature was 100° F., and his heart rate was 100 to 110 beats per minute.

On the twenty-second day in the hospital the patient again complained of shortness of breath, nausea and abdominal soreness. He began to cough up bright red blood. The heart sounds were distant, the pulse rate was 110 beats per minute, and the pulse was weak and thready. Râles were still present at the bases of both lungs. The abdomen revealed some shifting dullness. Digitalization was carried out rapidly by oral and intramuscular routes for two days and doses of this drug were given thereafter. Fluids were limited and diuresis was attempted. On the twenty-eighth day in the hospital respiration became labored and cyanosis appeared; the patient went into shock and died.

Postmortem examination revealed interstitial pneumonitis, extensive fibrinous pericarditis, toxic hepatitis, pulmonary hemorrhagic infarcts, and bilateral hydrothorax and ascites. The pericardial sac was adherent to the mediastinum and the adjacent surfaces of the lungs. The parietal pericardium was from 3 to 5 mm. thick. The epicardium and the pericardium were covered with a thick shaggy layer of fibrin and were partly adherent to each other. Free fluid was present in the spaces not obliterated by the adhesions. A roll of fibrin 9 by 5 by 3.5 cm. was lying along the left border of the heart. The myocardium was pale and soft. No changes were seen in the endocardium.

This case is representative of the occasional case of serious purulent pericarditis secondary to disease elsewhere in the body which is often fatal. Wise and Shafer [15] recently reported a case of purulent pericarditis cured by the intrapericardial injection of 40,000 Oxford units of penicillin. Our patient received a total of 3,840,000 Oxford units of penicillin parenterally during his illness and 255,000 units intrapericardially. The acute mediastinopericarditis seen in this case resembles that seen in chronic constrictive pericarditis.

Case 3. The patient, aged 18 years, was admitted to the hospital after he had fainted at muster. He had been well until two years before, when he had had intermittent fever for several months. The next year he had had a recurrence of the fever. Nine months before admission he was treated for measles and seven months before admission he had catarrhal fever. He had convalesced slowly from this, had continued to feel weak and had not regained his usual strength. His mother had died from tuberculosis when he was eight years of age.

In the hospital the temperature, pulse and respiration were normal and the patient gained weight. Repeated roentgenograms of the chest revealed mild fibrosis in the right medial portion of the lungs, extending upward from the hilum toward the clavicle (figure 4*A*). The fibrosis remained unchanged during the entire period of observation (figure 4*B*). Some cardiac enlargement was noted, but the ratio of the diameter of the heart to that of the thorax was 47 per cent and within normal limits. Repeated examinations of the sputum and concentrates of gastric washings were negative for tubercle bacilli.

The patient returned to duty feeling well after 118 days in the hospital. One week later, however, he noticed some shortness of breath. The morning of admission he complained of pain in the chest and had more severe dyspnea.

On examination dyspnea and cyanosis of the lips and fingernails were noted. The patient was restless and apprehensive and appeared extremely ill. Temperature was

102.6° F.; pulse rate was 104 beats per minute, and he had a paradoxical pulse. The blood pressure was 118 mm. Hg systolic and 88 mm. diastolic. The veins of the neck were distended. Cardiac dullness extended 5 cm. to the right of the sternum and to the left midaxillary line. The heart sounds were distant. No murmurs were heard. A pericardial rub was heard to the left of the lower portion of the sternum. The abdomen was slightly distended, and the liver was enlarged and tender. The remainder of the examination revealed no significant findings.

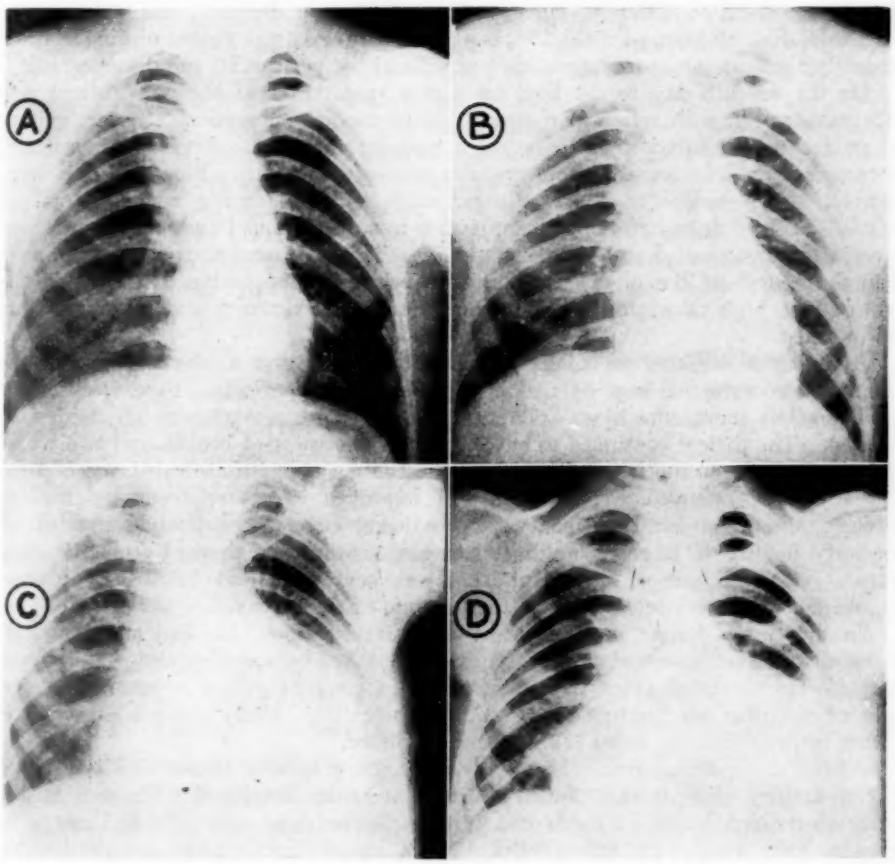

FIG. 4 (case 3). Gradual development of pericardial effusion which is typical of tuberculous pericarditis. *A*. April 28, 1944. *B*. August 18, 1944. *C*. September 6, 1944. *D*. November 2, 1944.

Laboratory studies revealed a value for hemoglobin of 65 per cent (Haden-Hauser test) and 3,400,000 erythrocytes and 4,450 leukocytes per cubic millimeter of blood. On differential count, 78 per cent of the leukocytes were polymorphonuclear cells, 20 per cent were lymphocytes and 2 per cent were eosinophiles. Moderate albuminuria was present. A bedside roentgenogram of the chest revealed the rather marked cardiac enlargement noted clinically (figure 4*C*), and a water bottle-like configuration. The transverse diameter of the heart measured 21.8 cm. and that of the chest was 30.5 cm. An electrocardiogram demonstrated tachycardia of sinus origin, and T-wave negativity in Leads I, II, III and IV.

The diagnosis was pericarditis with effusion, possibly tuberculous in origin.

The pericardium was at once aspirated and 400 c.c. of serosanguineous fluid were removed. This procedure gave relief. Examination of the fluid revealed five leukocytes per cubic millimeter; no organisms were seen on smear, and the culture was negative. The respiratory rate slowed and the paradoxical pulse disappeared. The patient was placed in an oxygen tent and treatment with penicillin was begun. Shortness of breath, precordial oppression and a weak rapid pulse were present again on the second day. A second aspiration yielded 450 c.c. of transudate. The arterial pressure increased to 130 mm. Hg systolic and 86 mm. diastolic, and the dyspnea decreased. Examination of the fluid was again negative as was guinea pig inoculation. Gradually signs of cardiac tamponade returned and the pericardial rub disappeared.

On the seventh day in the hospital a third aspiration of the pericardium was performed, again, with relief of dyspnea and precordial oppression. Smear, culture and guinea pig inoculation again revealed nothing abnormal. Fever continued and the record of the afternoon temperature was spiking in contour. Blood cultures were negative. After twelve days of treatment with penicillin during which a total of 2,880,000 Oxford units had been given, its use was discontinued and sulfadiazine was given in the dosage of 5 and later 4 gm. daily. This treatment too was discontinued when the course of the disease and fever continued. Supportive treatment in the form of rest, high caloric diet, blood transfusions, multivitamins and ferrous sulfate was initiated.

About three weeks after admission, fluid began to form in the left side of the thorax and rose to the level of the second interspace anteriorly. Five weeks after admission, left thoracentesis was done and 1,000 c.c. of serosanguineous fluid were removed. The patient continued to have moderate shortness of breath, and two weeks after the first thoracentesis the left side of the chest was again aspirated and 850 c.c. of yellow fluid removed. The patient felt improved. Another roentgenogram of the chest revealed a definite fluid level at the lower edge of the tip of the third rib anteriorly (figure 4*D*). An irregular band ran outward and upward from the right hilum. Ten days later a third aspiration was performed and 1,800 c.c. of serosanguineous fluid were removed from the left side of the thorax.

Gradually the patient became weak, listless and sallow. He had anorexia, epigastric distress and lost weight. Dyspnea was marked on exertion and was relieved by rest. He produced about one teaspoonful (4 c.c.) of yellow sputum daily and repeated examinations for tubercle bacilli were negative. Daily low-grade fever and spiking records of the evening temperature continued.

About 10 weeks after admission the abdomen gradually became distended and shifting dullness was present. Edema of the extremities developed. The patient was slowly digitalized, intake of fluids and salt was limited, and acid salts and mercurial diuretics were used with fair results. Three months after admission, abdominal paracentesis was performed and 1,020 c.c. of cloudy straw-colored fluid were removed. The patient became progressively worse. He had more shortness of breath, and fluid rapidly accumulated in the body cavities, except in the right side of the chest, and in the soft tissues. An electrocardiogram (figure 1*C*) revealed QRS complexes and T-waves of low voltage, which was suggestive of chronic pericarditis.

The patient had a characteristic attitude of distress, sitting upright in bed and leaning far forward. His venous pressure was 40 cm. of water. In order to prevent mechanical embarrassment of the heart by the accumulation of too much effusion, a fourth aspiration of the pericardium was done and 600 c.c. of fluid were removed, with relief to the patient. Guinea pig inoculation for the first time revealed tubercle bacilli. Abdominal paracenteses were performed as needed for relief of the distention. Owing to the recurring ascites, consultation with a thoracic surgeon was requested but it was decided that, in view of the persistent fever despite rest in bed and in view

of the activity of the infection, treatment should continue to be symptomatic and supportive. About five months after admission, a stained smear of the abdominal fluid revealed tubercle bacilli for the first time.

Gradually the patient began to feel somewhat improved and wished to be transferred to a hospital near home, and this was done. However, he continued to lose weight, and one day became irrational and developed signs of meningeal irritation.

The spinal fluid contained many leukocytes and the predominating cells were lymphocytes. He failed to improve and died.

Postmortem examination revealed tuberculous pericarditis, nodular tuberculosis of the tracheobronchial lymph nodes, localized lymphogenous miliary tuberculosis of the apex of the upper lobe of the right lung, acute tuberculous leptomeningitis, tuberculous ulcers of the ileum with involvement of the mesenteric lymph nodes, bilateral hydrothorax, ascites and edema of the legs.

Several large, soft, caseous tracheobronchial lymph nodes were matted with partial fixation of mediastinal structures near the superior portion of the pericardial sac. The pericardial surfaces were thick, shaggy, soft and pale yellow-green with only small ill-defined collections of free fluid. The heart had an estimated weight of 350 gm. without the pericardium, the visceral layer of which was 1 cm. in average thickness, including the shaggy exudate. Tubercles were seen near the myocardium in sections from the heart. No alterations were seen in any of the valves or in the deep myocardium.

The history of the insidious onset of the symptoms and the absence of pain suggested tuberculosis in this case, although the patient's contact with tuberculosis had occurred in the remote past. The development of large quantities of effusion over rather long periods of time is characteristic. The tuberculous origin in this case was proved when guinea pig inoculation with the pericardial fluid revealed tubercle bacilli, although repeated inoculations were necessary before the diagnosis was confirmed.

Comment

When the characteristic electrocardiographic pattern of acute pericarditis occurs, diffuse subepicardial myocarditis is present according to Burchell, Barnes and Mann.[16] When this process undergoes resolution and repair only slight thickening of the pericardium may remain, or with deeper and more extensive inflammation, adhesions between the layers of the pericardium and surrounding structures may result. The duration of acute pericarditis may vary from a few days to a few weeks, and it may recur [11] or chronic pericarditis may result, which may produce symptoms and signs after the lapse of some months or years.

The etiology of chronic constrictive pericarditis is of considerable interest and importance. Harrington[17] reported on five of 24 patients treated surgically for this condition. The clinical history and examination in these five cases, and microscopic study and culture made of the tissue removed at operation proved that the etiologic agent was tuberculosis. In the remaining 19 cases the type of primary infection was unknown. Eight of these 19 patients gave a history of one or more previous attacks of some pulmonary infection as pneumonia or influenza. Nine did not give a history

of any infectious process to which the condition could be attributed. These findings are in line with those reported by other workers.[18] In a follow-up study of 37 cases of constrictive pericarditis seen at the Massachusetts General Hospital, Harrison and White [3] reported that rheumatic fever is rarely, if ever, an etiologic factor.

Future observation of the patients who survived the episode of acute pericarditis would be most interesting for, as Broadbent [19] pointed out in 1895, "the key to the solution of adherent pericardium lies in watching cases of acute pericarditis as they go on to the formation of adhesions."

BIBLIOGRAPHY

1. White, P. D.: Heart disease, Ed. 2, 1937, The Macmillan Company, New York, pp. 461–468.
2. Kresky, P. J.: Suppurative pericarditis due to *Haemophilus influenzae* type B; a characteristic syndrome ushered in by symptoms of croup, Am. Jr. Dis. Child., 1943, lxv, 305–313.
3. Harrison, M. B., and White, P. D.: Chronic constrictive pericarditis; a follow-up study of 37 cases, Ann. Int. Med., 1942, xvii, 790–806.
4. Jager, B. V., and Ransmeier, J. C.: Constrictive pericarditis due to *Bacterium tularense;* report of a case and review of reported cases of pericarditis occurring with tularemia, Bull. Johns Hopkins Hosp., 1943, lxxii, 166–178.
5. Spear, P. W.: Fibrinous pericarditis following thyroidectomy, South. Med. Jr., 1938, xxxi, 215–218.
6. Wolff, Louis: Acute pericarditis simulating myocardial infarction, New England Jr. Med., 1944, ccxxx, 422–425.
7. Smith, H. L., and Willius, F. A.: Pericarditis. I. Chronic adherent pericarditis, Arch. Int. Med., 1932, l, 171–183.
8. Smith, H. L., and Willius, F. A.: Pericarditis. II. Calcification of pericardium, Arch. Int. Med., 1932, l, 184–191.
9. Smith, H. L., and Willius, F. A.: Pericarditis. III. Pericarditis with effusion, Arch. Int. Med., 1932, l, 192–202.
10. Willius, F. A.: Cardiac clinics, 1941, St. Louis, C. V. Mosby Company, p. 30.
11. Wolff, Louis: Acute pericarditis with special reference to changes in heart size, New England Jr. Med., 1943, ccxxix, 423–431.
12. Freedman, Eugene: Inflammatory diseases of the pericardium, Am. Jr. Roentgenol., 1939, xlii, 38–46.
13. Noth, P. H., and Barnes, A. R.: Electrocardiographic changes associated with pericarditis, Arch. Int. Med., 1940, lxv, 291–320.
14. Holt, Evelyn: Chronic adhesive pericarditis in childhood, Am. Jr. Med. Sci., 1929, clxxviii, 615–631.
15. Wise, A. W., and Shafer, L. E.: Purulent pericardial effusion treated with penicillin given intrapericardially, Jr. Am. Med. Assoc., 1945, cxxvii, 583.
16. Burchell, H. B., Barnes, A. R., and Mann, F. C.: Electrocardiographic picture of experimental localized pericarditis, Am. Heart Jr., 1939, xviii, 133–144.
17. Harrington, S. W.: Chronic constrictive pericarditis: partial pericardiectomy and epicardiolysis in 24 cases, Ann. Surg., 1944, cxx, 468–487.
18. Sprague, H. B., and White, P. D.: The indications for and results of pericardial resections—the course of five cases, Med. Clin. N. Am., 1932, xv, 909–917.
19. Broadbent, J. F. H.: Adherent pericardium, 1895, Bailière, Tindall & Cox, London, 126 pp.

TREATMENT OF HYPERTHYROIDISM WITH PROPYLTHIOURACIL *

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The current differences of opinion regarding the best form of treatment for hyperthyroidism are a reflection of the fact that of the several effective methods which are available, none is devoid of significant disadvantages. Experience with the use of antithyroid compounds is sufficient to show that this is a highly effective form of treatment, but extensive clinical trials have been carried out only with one such drug, thiouracil. The disadvantage attending the use of this compound relates almost exclusively to its side effects,[1] the drug fever syndrome or some variant of it and agranulocytosis. The former reaction usually precludes the continued use of the drug; the latter is of such severity as sometimes to cause death. These reactions together with milder ones less certainly related to the medication have been encountered in about one of every 10 patients treated with thiouracil.

With the aim of finding more satisfactory agents for clinical use many hundred compounds have been tested in animals. To date, the most active substance encountered has been propylthiouracil, and it has therefore been investigated in human beings.

This study is mainly concerned with the dosage of propylthiouracil in relation to the rate and to the degree of the metabolic response and with the incidence of untoward side effects. Other important considerations such as the general applicability of antithyroid drugs to the treatment of hyperthyroidism, the proper duration of treatment, the incidence of lasting remissions, and the effects of treatment on the condition of the eyes and of the thyroid gland are common to this and to other effective antithyroid compounds. As they do not bear specifically on this particular agent they will not be considered in detail here.

Clinical Material

This report is based upon observations on the first series of 100 cases to be treated with propylthiouracil. These cases were unselected, and the series comprises all cases of hyperthyroidism encountered during the 12 month period from April 1945, to April 1946. Preliminary data on the first 37 of these have already been published.[2] The 100 cases were made up of 80

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From the Joseph H. Pratt Diagnostic Hospital, the Boston Dispensary and the Department of Medicine, Tufts Medical School.

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Propylthiouracil was supplied by Dr. S. M. Hardy of the Lederle Laboratories, Inc., Pearl River, New York.

women and 20 men, 21 to 76 years of age. Fifty-seven had not previously received any form of therapy for hyperthyroidism, implying that these were either early cases or ones which had not been diagnosed formerly. Forty-three had been treated in the past either by operation, by iodine, by other antithyroid drugs, or by more than one of these methods. Subtotal thyroidectomy had been performed in 10 instances, two of which had had multiple operations. A total of 29 cases had at some time received iodine, and 21 of these had had iodine up to less than one month prior to the initiation of propylthiouracil therapy. Fifteen patients had had other antithyroid drugs, three of them more than one such drug. Of the seven instances of previous thiouracil medication, significant toxic manifestations had been noted in five; thiobarbital had been given to four patients, two of whom reacted unfavorably to it; ethylthiouracil had been used in seven instances without untoward effect.

Associated disorders and complications of hyperthyroidism were numerous. Thyrotoxic heart disease was diagnosed in 10 patients, five of whom had auricular fibrillation. Heart failure was considered to be due to rheumatic heart disease in three other persons. Three patients became pregnant and delivered normal children during the course of therapy. Other complications and associated disorders were: thyrotoxic myopathy, rheumatoid arthritis, diabetes mellitus, the menopause, obesity, cirrhosis of the liver or impaired liver function, peptic ulcer, pulmonary tuberculosis, thrombophlebitis, cholelithiasis, pernicious anemia, myasthenia gravis, spinal cord tumor, psychoneurosis and manic-depressive psychosis.

Therapeutic Procedure

With few exceptions, treatment was carried out without bed rest or significant restriction of activity. The exceptions were patients with heart failure and one with thyrotoxic myopathy who required rest. These and a few patients on whom special studies were being made were kept in the hospital for the first few weeks of treatment. Propylthiouracil was administered by mouth in the form of 25 mg. tablets at intervals of 8 or 12 hours. The initial dose was usually continued until all symptoms and signs of hyperthyroidism had disappeared. If, after a number of weeks, the rate of response was thought to be unduly slow, the dosage was increased and continued at the higher level until metabolic equilibrium was restored. Not until the patient had regained normal health was the dose reduced except in a few instances to be mentioned below. The maintenance doses were then continued for a minimum of six months. This arbitrary period of six months of normal health is probably a better estimate of the proper duration of treatment than one based upon the total period of therapy.

When propylthiouracil was being given other specific treatment was seldom used. When iodine had previously been given it was discontinued abruptly in most instances, but in severe cases it was gradually withdrawn

during the week or 10 days after propylthiouracil had been started. In two instances iodine in small doses was given for short periods during propylthiouracil therapy. These were cases with large vascular thyroid glands which exhibited further enlargement and increased vascularity during treatment. It should be noted these were the only cases in the series which experienced any significant thyroid enlargement during or after treatment. The only other therapy used was that prescribed for associated disorders such as heart failure, menopausal symptoms, etc.

No special diet or dietary supplements were provided, and none of the several agents which have been claimed to reduce the incidence of drug toxicity were employed. Frequent leukocyte counts were made only during the earlier part of the study. After some 50 patients had taken the drug without apparent harm, subsequent patients were not warned of any dangers associated with drug therapy. They were usually seen in the clinic or by their private physicians every few weeks until the hyperthyroidism was controlled and then at two to three month intervals thereafter.

Incidental to the study of this compound it has been found that the progress of the hyperthyroidism and the effects of treatment can be as well observed by the use of clinical criteria as by the frequent determination of the basal metabolic rate or the use of other special laboratory procedures. The dose can be properly adjusted on the basis of symptoms and such simple signs as the general appearance and behavior of the patient, the body weight, the pulse rate, the forcefulness of the heart beat, the condition of the skin, the steadiness of the hands and the size and vascularity of the thyroid gland. Excessive dosage is suggested by lethargy, sluggishness, an excessive gain in weight, a pasty and puffy appearance to the face and a conspicuous enlargement of the thyroid gland.

Dosage and Response

The earlier portion of this study was mainly concerned with a determination of the minimal effective dose. As a consequence, many patients received doses which later on were regarded as inadequate. A deliberate attempt was made to avoid excessive doses, and with few exceptions this aim was achieved. The majority of the first 70 cases received as an initial dose 25 mg. every eight hours. In one quarter of these the quantity was subsequently increased to 100 or 150 mg. daily. It was evident that, on the average, the rate of response to 75 mg. daily was slower than the rate of improvement with thiouracil in doses of 0.4 to 0.6 gm. daily. Also, it became clear that certain cases failed to be completely controlled by this dose even when it was continued for as long as five months. The majority of the last 30 cases included in this report received 100 or 150 mg. daily as an initial dose. The rate and degree of the response was significantly more satisfactory in this group.

An estimate of the minimal effective dose may be inferred from the data

shown in figure 1. In the upper diagram is shown the distribution of the initial doses employed in these 100 cases, while the lower diagram shows the maximal doses found necessary to restore metabolic equilibrium. The data reveal a considerable individual variation in dosage requirement. Fifty-seven per cent of the patients were eventually completely controlled by daily doses of 75 mg. or less, while in the remaining 43 per cent doses of 100 or 150 mg. were given initially or were found to be necessary later on in order to restore metabolic equilibrium.

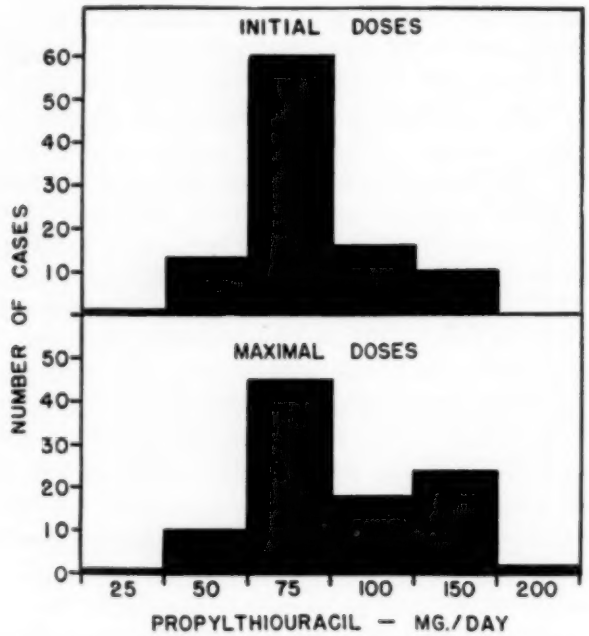

FIG. 1. The *upper diagram* shows the actual initial dosage used in the 100 cases. It varied from 25 to 200 mg. daily, but the majority of cases received 75 mg. The *lower diagram* shows the maximal dosage used during the entire period of treatment. A comparison of the two charts indicates that the arbitrary starting doses frequently had to be increased.

These findings, while pointing to the minimal doses which can be employed, do not provide a clear definition of the optimal dose for routine use. At present there is no method of determining in advance whether a given case will require a small or a large dose. An analysis of the individual patients summarized in figure 1 suggests that those requiring the larger doses were the more severe and more long-standing cases, those with large nodular glands and those who had taken prolonged courses of iodine. These criteria are not sufficiently reliable, however, to permit one to gauge the dose in all instances. It would be desirable to know the dose which would control all cases in a minimal period of time. This doubtless would be a larger dose than has been employed in this study, and one could safely predict that

its continued use would result in a troublesomely high incidence of myxedema if careful and frequent observations were not made. The use of larger doses in a routine manner would also have to await extensive clinical studies on the safety of larger amounts of this compound.

Confirmation of the impression that doses up to 150 mg. daily are not grossly excessive is provided by observations on maintenance doses and by the quantities which have been found to eventuate in hypothyroidism. Few patients were carried on the maximal dose of 150 mg. long enough to tell whether it would always lead to hypothyroidism. Three patients showed clear clinical evidence of hypothyroidism or an excessively elevated serum cholesterol after receiving 150 mg. daily for two and one-half, four or five

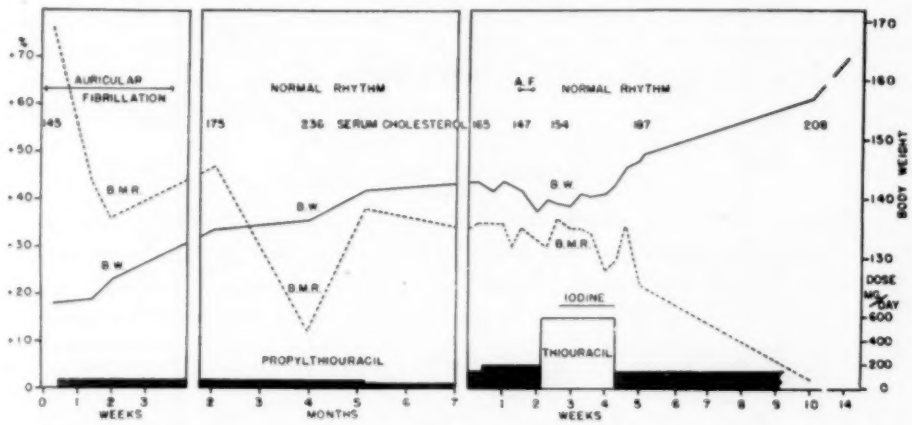

FIG. 2. Effects of various doses of propylthiouracil on the body weight, basal metabolic rate and serum cholesterol of a case of severe Graves' disease associated with advanced thyrotoxic myopathy and thyrotoxic heart disease with auricular fibrillation. This 53 year old man had been treated for two years as a case of lead poisoning because of the muscle paresis. Partial improvement had attended the use of potassium iodide. The initial metabolic response to 75 mg. daily of propylthiouracil was prompt and normal cardiac rhythm was restored in 18 days. When the dose was reduced to 50 mg. a relapse occurred which was only slowly brought under control with 150 mg. daily. Thiouracil in a dose of 0.6 gm. daily with full doses of Lugol's solution did not seem to be more effective than the propylthiouracil.

months respectively. Two developed hypothyroidism from 100 mg. daily, one from 50 mg. and one while taking 25 mg. This last case exhibited a marked rise in the serum cholesterol in addition to clinical evidence of early myxedema eight months after treatment started and four months after the dose had been reduced to 25 mg. daily. Whether this represents an unusually striking response to the drug or whether it was a spontaneous hypothyroidism cannot be determined.

This study of dosage leads to the conclusion that 150 mg. daily is an appropriate initial dose for severe and moderately severe cases of hyperthyroidism and that, although many cases would respond to less, smaller doses such as 75 or 100 mg. daily might best be used only in milder forms of the disease. The initial dose should be continued until all manifestations

of the disorder have disappeared, and only then should it be reduced to 100 or to 50 mg. daily. Later on, during the maintenance period, the quantity given daily can further be reduced to 50 or 25 mg.

Two of the most difficult cases encountered in this series are summarized in figures 2 and 3. The responses of these two patients illustrate several points of importance. In each instance a small initial dose brought about a

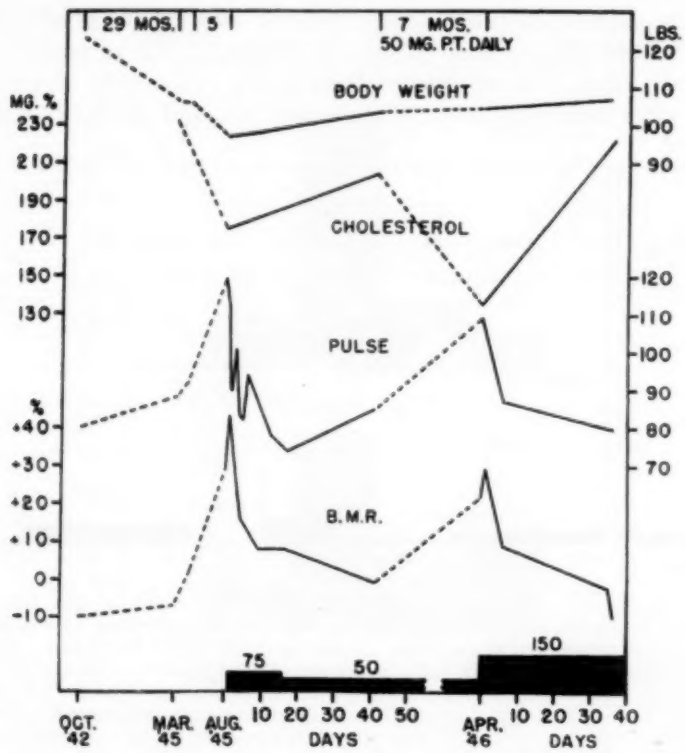

FIG. 3. The course of a patient treated with propylthiouracil illustrating the difficulty in determining the minimal effective dose. This 53 year old woman was treated in the hospital for a fractured wrist in 1942 before any evidence of hyperthyroidism was evident. She entered the hospital again in March 1945, because of recurrent bouts of diarrhea, weight loss, easy fatigue, nervousness and sweating. The diagnosis was not made until a subsequent admission five months later. Propylthiouracil in a dose of 75 mg. daily brought about prompt and striking improvement. During a seven month residence in Florida 50 mg. daily failed to maintain the remission, and 150 mg. daily were used to evoke a second response which, though more complete, was no more rapid than that induced by 100 mg. daily. A maintenance dose of 100 mg. daily subsequently seemed to be required.

prompt though incomplete response. In both cases the dose was reduced before complete health had been restored, and when hyperthyroidism had returned, prolonged treatment with a large dose was required to restore normal health. In retrospect it is apparent that a larger initial dose continued for a longer time would have given a more satisfactory result.

The well recognized influence of previous iodine therapy in delaying the

clinical response to an antithyroid drug was observed in a number of instances in this series. A minority of patients recently under the influence of iodine exhibit a prompt response to antithyroid therapy, and consequently the greater variation in the rate of response of iodine-treated patients makes them less suitable for evaluating the effectiveness of a new drug. The extremes noted in this series were as follows. The most rapid response was seen in a woman of 28 who had received iodine for four months; prompt improvement occurred when iodine was started but control was only partial; when a skin eruption developed the iodine was discontinued, and four days later propylthiouracil was given in a dose of 150 mg. daily; within two weeks all residual manifestations of hyperthyroidism had disappeared. The longest iodine-induced delay occurred in a woman of 52 who despite full doses of iodine for four years had remained severely thyrotoxic; the iodine was discontinued when propylthiouracil was started; a dose of 150 mg. daily was continued for three months before a distinct improvement was apparent, but subsequently recovery was rapid.

Side Effects

In this series of cases no significant side effects were encountered. As in any group of patients under observation for prolonged periods of time, minor illnesses of one kind or another developed in some during the course of therapy. With the possible exception of itching of the skin with or without a mild urticarial rash, these intercurrent episodes followed no recognizable pattern, but some of them may have been caused by the drug.

Transient itching of the skin was noted by four patients, and in two of these a frank urticarial eruption was seen. In only one instance was the drug stopped, but in this case treatment was resumed 48 hours later and continued for three months without a recurrence of symptoms. In the others the itching subsided within a few days without withdrawing the medication. It is significant that itching of the skin was complained of by three patients before the treatment was started. Two patients complained of headache during the first few days of therapy. They considered that the headache was unusual for them and felt that the medication was responsible. In one the drug was omitted for 36 hours, but the headache continued until two days after it was resumed. Thereafter the headache did not return. The second patient continued the medication and the headache cleared in four days. One man developed what appeared to be an acute upper respiratory infection during the second month of treatment. There was a severe sore throat and a temperature of 100.5° F., but the leukocyte count remained normal; other members of the family had a similar disorder. Medication was not interrupted and recovery was complete in five days. A month later he complained of migratory joint pains involving one hip, the knees and the ankles. As he had suffered from subdeltoid bursitis prior to treatment, the arthralgia was not considered to be caused by the drug. Therapy was continued, and when

the hyperthyroidism was completely controlled the joints improved and he remained symptom-free during the ensuing four months of treatment.

One patient died while being given propylthiouracil. This man of 52 with advanced cirrhosis of the liver was thought to have hyperthyroidism as well, and propylthiouracil in a dose of 75 mg. daily was administered. The clinical course was that of progressive hepatic failure; the introduction of propylthiouracil therapy did not seem to modify the condition one way or the other, and he died in hepatic coma three months after treatment was started.

In retrospect it would appear likely that most of these episodes were unrelated to propylthiouracil therapy, but it is possible that the two episodes of urticarial eruption were manifestations of drug sensitivity. The significant finding was that no serious reactions occurred and that in no instance was it necessary to abandon this form of treatment.

Particularly instructive were the patients who had previously exhibited intolerance to thiouracil and to thiobarbital. Five patients were given propylthiouracil after they had experienced severe febrile reactions to thiouracil. In two of these the fever had been accompanied by significant neutropenia. One of these patients and one other had had febrile reactions accompanied by an extensive skin rash following the use of thiobarbital. In none of these six patients were any untoward effects observed following the use of propylthiouracil.

It is also of interest that three of the patients in this series of 100 were referred for treatment because of intolerance to iodine. Each of these was treated with propylthiouracil without mishap.

Doubtless some sensitivity reactions will be encountered if this compound is extensively employed. There are few drugs which when continually administered do not provoke untoward reactions in a certain percentage of individuals. However, in the therapy of a serious disease the absence of significant side effects in 100 consecutive cases indicates that the risk attending the use of this drug is not a material consideration.

Summary

One hundred unselected cases of hyperthyroidism encountered during the course of one year were treated with propylthiouracil. Considerable individual variation in the minimal effective dose was observed, some patients requiring as little as 50 and some others as much as 150 mg. daily to restore metabolic equilibrium. It was concluded that 50 mg. every eight hours is approximately the optimal dose for the routine treatment of the more severe cases, that 50 mg. twice daily is adequate for milder ones, and that an effective dose should be continued until all manifestations of the disease have been controlled before smaller maintenance doses are substituted.

The use of this medication was unattended by significant side effects, and it is therefore suggested that it is a safe and satisfactory compound for the treatment of hyperthyroidism.

ACKNOWLEDGMENT

We are indebted to the many physicians who have permitted us to include their private patients in this study and to the staffs of the Pratt Hospital and Boston Dispensary for their generous assistance.

BIBLIOGRAPHY

1. VAN WINKLE, W., HARDY, S. M., HAZEL, G. R., HINES, D. C., NEWCOMER, H. S., SHARP, E. A., and SISK, W. N.: The clinical toxicity of thiouracil, a survey of 5,745 cases, Jr. Am. Med. Assoc., 1946, cxxx, 343.
2. ASTWOOD, E. B., and VANDERLAAN, W. P.: Thiouracil derivatives of greater activity for the treatment of hyperthyroidism, Jr. Clin. Endocrinol., 1945, v, 424.

OBSERVATIONS ON THE USE OF THIOURACIL *

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IN the two and one half years that have elapsed since Astwood's [1] discovery and use of the potent agent, thiouracil, numerous investigators have fully confirmed his original observations and have added much useful data regarding the behavior of this chemical substance. This invested effort is now beginning to show returns in increased interest in and better understanding of the general nature of its action on the thyroid, and in a growing recognition of the value of thiouracil for combating the thyrotoxic state and reducing it to a safe tractable level.

A number of facts regarding thiouracil appear to be generally accepted. The best explanation of the action of thiouracil is that it interposes a block at the acinar cell of the thyroid stopping production of thyroxin. This action unbalances the normal reciprocal relationship between the thyroid and the anterior pituitary whereby the production of thyroxin and of thyrotropic hormone are each determined by the quantity of the other of these hormones in the circulation. As the amount of thyroxin diminishes, increasing quantities of thyrotropic hormone are elaborated which stimulate hyperplasia of the acinar cell but without increasing the production of thyroxin. A measurable change in the body metabolism occurs only after all of the pre-formed thyroxin has been used up, thereby explaining the delay in appearance of drug action.

Thiouracil-induced hyperplasia differs from that induced by the cyanides in that it is not at all influenced by iodine, although it may be retarded by previously administered iodine stored as thyroxin, which tends to inhibit the pituitary. Thiouracil-treated rats fed radioactive iodine show very little formation of diiodotyrosine and thyroxin, but when thiouracil is withdrawn, the amount of radioactive iodine converted to thyroxin increases, the full concentrating capacity of the thyroid being restored in about 14 days after withdrawal of the thiouracil.

Thiouracil is rapidly absorbed from the intestinal tract, reaching a peak blood level in 15 to 30 minutes after 0.1 to 0.2 gm. has been administered to a normal fasting man. From this point there is a gradual decline in the blood level with complete disappearance in 48 to 72 hours. The blood concentration may be maintained fairly well by repeated frequent administration of small doses. The drug enters the cellular elements rapidly, the quantity in the red blood corpuscles being approximately twice that of the

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The thiouracil was supplied through the courtesy of Dr. Stanton M. Hardy, Lederle Laboratories, Inc.

leukocytes, but proportionately higher in the latter than in the former. Bone marrow attracts the largest proportion of the drug, the thyroid, ovaries and pituitary holding lesser amounts in the order mentioned. Alterations of thyroid structure affect drug storage so that more is stored in adenomatous than in normal tissue. A large part of ingested thiouracil is rapidly destroyed in the intestinal tract so that none is found in the stools. The remainder is excreted mainly in the urine.

Very few tissue changes other than the characteristic hyperplasia in the thyroid gland have been observed. The McKenzies [3] noted basophilia ("thyroidectomy cells") in the anterior pituitary of thiouracil-treated animals, and a similar finding was reported recently by the author [4] in the case of a woman who died suddenly of cerebellar hemorrhage while she was under treatment with thiouracil for toxic thyroadenoma.

Benign and malignant tumors of the thyroid have been produced in rats by the combined administration of allylthiourea and a carcinogen, 2-acetyl aminofluorene, but neither of these substances was capable of inducing thyroid neoplasia alone. It is significant that up to the present there have been no reports of malignant changes occurring either in animals or man as a result of the administration of thiouracil or thiourea.

Clinical Experience

Although 91 patients have been treated with thiouracil during the past two and one half years, only 70 have been observed for a sufficient period to permit drawing definite conclusions from the experience. Of the remaining 21, only five had thyrotoxicosis, but these had been treated for too short a time. The rest consisted of three cases of questionable hyperthyroidism, three of hyperthyroidism induced by overfeeding with thyroid substance, three instances of thyroiditis, and seven patients with angina pectoris (not included in this report).

The 70 patients with thyrotoxicosis ranged in age from 16 to 82. Forty of these had toxic adenoma, the group consisting of 10 males and 30 females. There were 30 patients with toxic diffuse goiter, five of these being males and 25 females. The average initial basal metabolic rate was plus 26 per cent for those with toxic adenomata and plus 30 per cent for the toxic diffuse goiters. In this latter group 16 patients had had previous thyroidectomies, 11 having had one, 3 two, and 2 three.

Dosage of Drug

Early in this study patients were given 0.8 gm. of the drug daily, divided into four equal doses of 0.2 gm. This was in keeping with the generally recommended dosage of 0.8 gm. to 1.2 gm. per day. As it became recognized that large doses offered no special advantage, the daily amount was reduced to 0.6 gm. per day, and now the average daily initial dose is between 0.4 and 0.6 gm. It is best that the interval between doses not be prolonged

beyond 12 hours. Response to the drug was satisfactory in all except one, a patient with diabetes mellitus and toxic adenoma who had been under treatment with iodine for six years before starting thiouracil. After 17 months' administration of thiouracil without response, it was replaced by 0.6 gm. thiourea daily for the next three months, but without notable effect. It is quite likely that this failure may have been due to the long continued previous administration of iodine which interfered with the absorption of the thioureas. The experience of other investigators indicates a failure in about 2 per cent of treated cases, with the cause not always evident.

Most patients reported subjective improvement within one to two weeks after beginning treatment, but objective signs of response appeared after a somewhat longer interval. Of the patients who had had iodine, those with toxic diffuse goiter required an average of 8.2 weeks before responding satisfactorily, while those with toxic adenoma required but 6.6 weeks. Where there was no previous treatment, the former (toxic diffuse) took 6.6 weeks whereas the latter took six weeks. The patients who had had previous operation required an average of 6.2 weeks before remission appeared. These figures vary somewhat from the reported experience which credits toxic diffuse goiter patients and those previously untreated with iodine with an earlier response. Generally, however, six to seven weeks may be considered as the shortest period in which to expect a remission.

As improvement appeared, dosage was reduced. The initial 0.6 gm. daily dose was reduced to 0.4 gm. after three to five weeks; and as remission gradually became manifest, a maintenance dose was given that would keep the patient in continuous remission without causing myxedema. In the group under observation 22 are now on a maintenance dose of 0.1 gm., 19 on 0.2 gm., 17 on 0.3 gm., 9 on 0.4 gm. and 3 on 0.6 gm. daily.

Twenty-five patients have been treated from two to six months, 25 more from seven to 12 months, 16 patients from 12 to 24 months and four from 25 to 28 months. Repeated attempts have been made to determine whether the drug may be discontinued and when it is advisable to do so. In every instance in which this was attempted before six months' treatment had been carried out, relapse occurred after an interval of three days to eight weeks. Ten patients, six with toxic adenoma and four with toxic diffuse goiter, have remained in remission for periods ranging from six to 24 months. It is significant that the period of treatment in these patients was not less than six months, the average being 13 months. Although some investigators claim sustained remission in a large number of treated patients, the average of those who continue in remission after the drug has been stopped is approximately 10 per cent. Nevertheless, it is worthwhile to discontinue the drug after from 18 to 26 weeks. If relapse occurs, its readministration brings patients back into line quite promptly.

A basal metabolic rate between plus 5 and minus 10 per cent was desirable, but was not easily maintained, particularly in those with toxic diffuse goiter. Mild grades of myxedema developed in four with toxic diffuse

goiters and two with toxic adenomata. The basal metabolic rate dropped to minus 14, 17, 27 and 32 in the former and minus 23 and 24 in the latter. Prompt recovery followed cessation of the drug for one week followed by resumption at a lower dosage level. These patients are now being given small doses of thyroid substance, ranging from ¼ to ½ grain daily, in addition to the thiouracil. This appears to be a logical supplementary treatment in patients who are being given thiouracil for extended periods of time. Here it is conceivable that an increasing need for thyroxin may develop because of the possible total suppression of its production. Accordingly, the exhibition of small amounts of thyroid substance after the overactive thyroid gland has been depressed by thiouracil appears logical where prolonged medical treatment is planned. Early concomitant administration with thiouracil is not advisable, but rather it is preferable to begin after remission has become fully manifest. Twelve patients in this series are now on combined therapy; seven have toxic diffuse goiters, while five have toxic adenomata.

Changes in the Thyroid Gland

Some increase in size of the thyroid was noted in the early weeks of treatment and was usually associated with softening of the gland. These changes were more pronounced in the toxic diffuse goiters, but in either type they rarely reached alarming proportions. This enlargement caused tracheal compression in three patients with large adenomata and in one instance hemorrhage into the gland was found at operation. Gradually, however, the gland tended to recede and become smaller and in many instances has diminished in size remarkably though it has never become totally impalpable.

Exophthalmos

Slight increase in exophthalmos was observed in only one patient during treatment, and this has remained stationary after subtotal thyroidectomy. Of nine patients with post-operative residual hyperthyroidism and exophthalmos, three showed no change in the exophthalmos while six showed measurable improvement.

Thyrotoxic Auricular Fibrillation

Four patients with thyrotoxic auricular fibrillation, all taking digitalis, showed a return to normal sinus rhythm as soon as the thyrotoxic state was controlled by thiouracil. None of these patients have had further need for digitalis. Obviously, where the fibrillation is secondary to disturbances other than thyrotoxicosis, satisfactory control is not to be expected.

Reactions

Unfavorable reactions to thiouracil have been quite thoroughly publicized, and rightfully so, since this is a new drug, potent in action, with

harmful potentialities in some of its side effects. Indiscriminate condemnation is not indicated by these warnings. Rather are they to be taken as cautionary guides in the proper use of this potent but valuable drug.

Agranulocytosis has been the outstanding unfavorable reaction, with drug fever ranking next as a serious disturber. The former complication is likely to occur without warning and without previous leukopenia or granulocytopenia. The unpredictability of its appearance, together with the established belief that fatalities run close to 100 per cent, has caused many to shun even mention of thiouracil. However, the danger has been exaggerated. Although this is an alarming complication, its incidence is no higher than 2.5 per cent and its mortality 10 to 12 per cent. In fact, the mortality from agranulocytosis in all thiouracil treated cases is 0.4 per cent, and its further reduction is fully expected now that it has been found that cessation of administration of the drug and continuous parenteral administration of penicillin will allow the patient's bone marrow to recover from its suppression without the intervention of fatal infection. One patient in this series developed agranulocytosis on the fifty-ninth day after she had had 10.1 gm. of thiouracil. Recovery followed after one week of continuous penicillin therapy.

Unfortunately there is no known method of prevention. Large doses of vitamin concentrates, pyridoxine, folic acid and liver extract have all been tried without avail. We tried testing 100 people intradermally with serum obtained from a patient under treatment with thiouracil (with a serum level of 3 to 4 mg. per cent) but dropped the investigation when no reactions were noted, particularly in one patient who had had two separate episodes of drug fever from oral thiouracil.

At present the only safe procedure to follow is to observe patients at regular intervals, making blood counts at first every week and later every two to four weeks, and making certain that these patients do not travel away from home, placing themselves out of reach.

One significant observation is the seeming preponderance of patients with toxic diffuse goiter among those developing agranulocytosis. Correspondence with 10 of the leading investigators in the field and a survey of the reported cases of this complication substantiate this finding. The obvious inference is that patients with toxic diffuse goiter, being more prone to this disturbance, must be watched more closely while under treatment.

Five patients in this series developed drug fever with chills, malaise and sore throat but without change in the blood picture, after varying periods of drug administration. One developed the reaction during the thirty-sixth week and one each after 14, 8, 7, and 3 days. A subsequent trial with a small dose of the drug produced the same reaction, so that its use was abandoned in all of these patients. Two patients developed a generalized urticarial eruption which cleared within a few days after the drug was discontinued.

Induced Hyperthyroidism

Hyperthyroidism induced by overtreatment with thyroid substance appears to respond quite promptly to thiouracil therapy. Three instances have been observed.

Case Reports

The first, a man aged 47, with a reported basal metabolic rate of minus 30 per cent, had been taking 6 gr. thyroid substance because of sexual impotence for a period of six weeks. He had lost 10 pounds, was nervous and irritable, with palpitation and tremor, and the basal metabolic rate was plus 22 per cent. The thyroid gland was not palpable. Disappearance of all symptoms with gain in weight and return of the basal metabolic rate to a normal level occurred after eight weeks of thiouracil (0.4 gm. daily).

The second patient, a man aged 38, had been taking 3 gr. thyroid substance daily for six months because of tiredness, backache and a low basal metabolic rate. He lost weight, had tachycardia, and in spite of replacement of thyroid substance by Lugol's solution, developed auricular fibrillation. This continued uncontrolled for four months until he was started on thiouracil. After two weeks, normal sinus rhythm had been reëstablished and the basal metabolic rate had dropped from plus 39 per cent to plus 21 per cent. A slight enlargement of the thyroid was found. He remained under control during the next nine months while taking 0.2 gm. thiouracil daily, but when this was discontinued, his symptoms recurred at the end of four weeks and he is still obliged to take 0.1 gm. daily to remain in remission.

The third patient, a woman aged 35, was for some fantastic reason placed on 32 gr. thyroid substance daily following a double mastectomy for cystic mastitis. She became extremely nervous and irritable, was constantly hungry and had marked urinary frequency. This unusual treatment was followed for six months. Then the dosage was reduced and kept at from 21 to 28 gr. thyroid substance daily for the next 3½ years. At this point the patient decided she was not improving and stopped the medication.

When first seen she had had no medication for two weeks. She was extremely nervous and restless, had a fine tremor of the hands, but showed no thyroid enlargement, eye signs or tachycardia. The basal metabolic rate was plus 13 per cent. After four weeks on 0.4 gm. thiouracil daily she gained five pounds, the basal metabolic rate was plus 5 per cent and the original symptoms were much less pronounced. Gradually the drowsiness, urinary frequency, and, finally, the extreme hunger, disappeared after three months' treatment.

Diabetes Mellitus and Hyperthyroidism

In the past this serious combination has been controlled with varying success either by thyroidectomy, when the patient could be stabilized sufficiently to withstand operation, or by use of iodine. The positive action of thiouracil in thyrotoxicosis early suggested its use in this combined disturbance, but reports on its use are variable insofar as the expected improvement in the diabetes is concerned.

Eight patients with this condition have been treated with thiouracil. These ranged in age from 27 to 66; five were females, and three males. In one patient both the thyrotoxicosis and diabetes had been successfully controlled by iodine. In this case there was no response to thiouracil. Four

of the remaining seven patients also showed a marked improvement in their diabetes as evidenced by levelling of blood sugar fluctuations, absence of glycosuria, and reduction in dosage or total elimination of insulin. The remaining three, although developing satisfactory remission in the thyrotoxicosis, failed to show improvement in the diabetes. The reason for this difference in reaction became apparent when it was noted that all patients in the first group had toxic adenoma or secondary hyperthyroidism, the diabetes having preceded the thyrotoxicosis. The patients in the second group all had toxic diffuse goiters (two with previous thyroidectomy) or primary hyperthyroidism, which had appeared before the diabetes.

When the case reports in the literature were restudied and classified[5] there were 13 treated patients of whom four had improved whereas nine had not. The patients improved were all instances of toxic adenoma whereas the others had toxic diffuse goiter.

Pre- and Post-Operative Use of Thiouracil

Eleven patients in this series were subjected to thyroidectomy after previous preparation with thiouracil. Five of these had toxic diffuse goiter and six toxic adenoma. Before the combined use of thiouracil and iodine was recommended by Bartels and Lahey, patients were prepared with thiouracil alone. The surgeons encountered varying degrees of increased vascularity and friability in all instances, least notable in those brought to a full state of remission before operation.

Two patients prepared with thiouracil and iodine developed myxedema on the second and third post-operative day. In all probability the level of thyroxin production was quite low at operation, and the myxedematous state may well have been precipitated by the resection of the gland and the temporary functional depression of the residual tissue. Improvement in these patients followed promptly on the administration of small amounts of thyroid substance. Two patients with fulminant toxic diffuse goiters uninfluenced by iodine responded only slowly to thiouracil. In each instance, the addition of iodine after four months of thiouracil produced a summation of effect and permitted preparation for and performance of thyroidectomy. Surgeons are generally agreed that patients prepared with thiouracil constitute as slight a risk as those with non-toxic adenoma and their post-operative course is as smooth and uneventful.

Sixteen patients in this series had had thyroidectomy previous to treatment with thiouracil, three having had two and two having had three operations. All of these patients originally had true Graves' disease. Response to thiouracil was both prompt and satisfactory in all of these patients although many had been taking iodine without improvement for varying periods of time. In four, a second thyroidectomy was under consideration but was deferred because of the improvement. In none of these patients, however, has it been possible to discontinue the drug without a return of symptoms, although

some of them have been under treatment for nearly two years. It is apparent that here the original causative factor is uninfluenced by the thiouracil which controls only the effect.

Acute Thyroiditis

In the past, patients presenting this rare complication remained ill for a protracted period with marked tenderness and swelling over the thyroid, difficulty in swallowing, fever, palpitation and elevated basal metabolism. Treatment consisted mainly of local application of ice, administration of Lugol's solution and roentgen therapy. Relief was slow and protracted, often taking several months. In some instances suppuration necessitated surgical drainage. The advent of thiouracil has changed this picture appreciably. King and Rosellini [2] were the first to call attention to the promptness with which acute thyroiditis subsides when thiouracil is administered, eight of their eleven patients having been promptly cured.

Three patients in this series had acute thyroiditis which subsided promptly following thiouracil administration. All had been treated symptomatically with iodine and local application of ice for varying periods of time. The condition subsided in 8, 10, and 14 days respectively, and the thyroid enlargement in the first two patients disappeared completely at the end of three months. Thyroidectomy was performed on the third patient at the end of two months for an adenoma that had been present for 20 years.

Disease Tested with the Drug

As with any potent therapeutic drug, there arise instances in which the procedure may be reversed, and instead of testing the drug against the disease, the latter, particularly if it is borderline or questionable, is tested with the drug. Clinically, a variety of disturbances with certain characteristics simulating hyperthyroidism present themselves for accurate diagnosis. These occur mainly in patients with anxiety neuroses or in those with neurocirculatory asthenia. The occult forms of hyperthyroidism responsible for auricular fibrillation or accentuating diabetes mellitus also belong in this group.

In the past iodine has been used in these patients with varying success, and it was thought that a more potent depressive agent such as thiouracil might prove more useful and decisive. Accordingly, the drug was used in several patients in whom a diagnosis of hyperthyroidism was thought likely but in whom many of the distinctive features were lacking.

The first of these was a 39 year old white male complaining of insomnia, nervousness, palpitation, tremor of the hands and a weight loss of six pounds during a period of six months. He presented no thyroid enlargement or eye signs, but the palms were warm and moist, there was tachycardia, and the basal metabolic rate was plus 7 per cent. Because of a history of domestic and financial difficulties and because of heavy use of tobacco, it was felt that this was an anxiety state coupled with symptoms of chronic tabagism. However, to rule out the presence of a thyrotoxic com-

ponent a daily dose of 0.4 gm. thiouracil was administered during a period of nine weeks. The basal metabolic rate readings at two week intervals were plus 4, plus 6, zero and plus 2 and no improvement was noted in the patient's condition.

A second patient, a 42 year old white unmarried woman, had been under observation for a year because of exhaustion, nervousness, insomnia, palpitation and cold clammy hands and feet. She was 66½ inches tall and weighed 111 pounds. There was scoliosis of the thoracic spine, and the lower pole of the right kidney was movable and palpable. The blood pressure was 100 mm. Hg systolic, 60 mm. diastolic. After the usual therapy for neurocirculatory asthenia had produced little improvement, a trial of thiouracil was instituted. The thyroid was not palpable, and there were no eye signs present. The basal metabolic rate was minus 3 per cent. She tolerated 0.6 gm. of thiouracil daily for a period of three months with no improvement in her general condition. The final basal metabolic rate reading was minus 17 per cent.

The third patient, seen only recently, was a white woman aged 56, with diabetes mellitus that was extremely difficult to control (she required as much as 200 units insulin per day) who was found to have a small palpable nodule in the right lobe of the thyroid and a basal metabolic rate of plus 10 per cent. There were no other signs of hyperthyroidism, but it was believed worthwhile to use thiouracil to determine whether this was present. The response was quite dramatic. Within two weeks, on 0.4 gm. per day, the basal metabolic rate had dropped to plus 5 per cent, the thyroid nodule was larger and softer, and the blood sugar had fallen to 150 mg. per cent on only 40 units insulin daily.

Evidently thiouracil can serve usefully in the differentiation of borderline disturbances, but its administration in such conditions must be carefully watched and limited to as short a period as is essential for arriving at a definite diagnosis.

Summary and Conclusions

From the observations reported here and those of other workers in the field, the following conclusions regarding thiouracil appear valid and firmly founded:

1. The drug is a potent thyroid-depressing agent which blocks the acinar cells of the thyroid, preventing the formation of thyroxin and indirectly liberating excess thyrotropic hormone from the anterior pituitary, causing marked thyroid hyperplasia. When its action is fully established there occurs a basophilia in the anterior pituitary similar to that which follows thyroidectomy.

2. It is effective in both toxic adenoma and toxic diffuse goiter asserting its full action after an average of six weeks of administration. Previous administration of iodine appears to retard the action somewhat. Failures occur in about 2 per cent of treated patients.

3. Permanent remission occurs only in about 10 per cent of patients after stopping the drug. The remainder tend to relapse after a varying period of time. The relapse rate is highest in those patients who have been treated for less than 18 to 26 weeks. At present it is still not possible to predict how long a period of treatment is necessary for inducing permanent remission.

4. Myxedema may readily follow the use of thiouracil, but this may be promptly alleviated by stopping the drug for a short time and administering small quantities of thyroid substance. In fact it would appear logical, during the prolonged use of thiouracil, to administer thyroid substance also, thus supplying the body with its minimal need for this agent.

5. Some increase in size of the thyroid, as well as softening, occurs in many instances. Rarely there is a rapid increase in size with resultant pressure symptoms. Ultimately the gland tends to recede and become smaller.

6. Exophthalmos is rarely increased. In fact, six of nine patients with this condition present before treatment showed improvement.

7. Thyrocardiacs with auricular fibrillation show a return to normal sinus rhythm if the disturbance is caused only by thyrotoxicosis.

8. Toxic reactions occur in about 13 per cent of treated cases. Agranulocytosis, the most serious reaction, has an incidence of 2.5 per cent and a mortality rate of 10 to 12 per cent which probably will be reduced by treatment with penicillin administered parenterally. It appears most likely to occur in patients with toxic diffuse goiter, so that this group of patients requires close watching. Drug fever is next in incidence and appears to be an expression of drug idiosyncrasy. Patients showing this reaction are usually unable to take the drug.

9. It is especially useful in hyperthyroidism induced by overdosage with thyroid substance; in diabetes mellitus complicated by hyperthyroidism; in acute thyroiditis; and as a diagnostic aid in borderline hyperthyroidism.

10. It is today the most effective agent for inducing remission in thyrotoxicosis and has proved itself extremely useful in the preparation of patients for thyroidectomy, making for simpler, less costly pre-operative preparation and smoother shorter convalescence.

Evaluation of its use medically can not be made as readily at the present time because of the tendency to relapse after cessation of treatment and the limited knowledge regarding toxicity. However, it has a dominant place in the treatment of the aged patient with toxic adenoma who is a poor operative risk, and in those with recurrent thyrotoxicosis. Only time will tell whether it will ultimately become the treatment of choice in toxic diffuse goiter.

BIBLIOGRAPHY

1. Astwood, E. B.: Treatment of hyperthyroidism with thiourea and thiouracil, Jr. Am. Med. Assoc., 1943, cxxii, 78.
2. King, B. T., and Rosellini, L. J.: Treatment of acute thyroiditis with thiouracil, Jr. Am. Med. Assoc., 1945, cxxix, 267.
3. MacKenzie, C. G., and MacKenzie, Julia B.: Sulfonamides, thioureas and thyroid, Endocrinology, 1943, xxxii, 185.
4. Reveno, W. S.: Effect of thiouracil on human tissues, Jr. Clin. Endocrinol., 1945, v, 403.
5. Reveno, W. S.: Thiouracil effect in diabetes mellitus complicated by hyperthyroidism, Am. Jr. Med. Sci., 1946, ccxi, 174.

THE DIAMIDINES IN CHEMOTHERAPY: A SURVEY OF RECENT DEVELOPMENTS WITH A NOTE REGARDING THERAPEUTIC TRIALS IN PATIENTS WITH RHEUMATOID ARTHRITIS *

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RECENT advances in the field of therapy for protozoal diseases, though not so spectacular as the discoveries of sulfonamides and penicillin, have nevertheless been significant and deserving of wider attention than they have yet received in this country.

The most interesting and most promising of these discoveries concerns the parasiticidal effects of the family of strongly basic organic preparations known as diamidines. These compounds have been shown to possess value in treatment of leishmaniasis and trypanosomiasis, diseases which affect many inhabitants of great portions of the earth and cause endless suffering. Compounds of this group also possess bactericidal properties, and for this reason there is hope that further important uses may be found for these drugs.

HISTORICAL

Behind the development of these compounds lies an interesting story of a scientific search which followed a tenuous thread of information for nearly 30 years and finally led to a discovery which may prove to be momentous.

The story of this search was told by Professor Warrington Yorke [35] in an address delivered at a meeting of the Royal Society of Tropical Medicine and Hygiene in 1940. His story illustrates a strange and provocative paradox: in the field of scientific research even a misconception may, at times, lead to important discoveries.

As early as 1911, trypanosomes were observed to survive longer in citrated blood if glucose was added to the medium, and later it was shown that trypanosomes require relatively large amounts of glucose for maintenance and growth. Cultured in citrated blood these organisms gradually became motionless and died, but inanimate, apparently moribund organisms, could be reanimated by the addition of blood serum or glucose-containing solutions to the medium. A study of this phenomenon showed that glucose was the substance responsible for reanimation of the inanimate organisms.

It was also found that in the terminal phases of experimental trypano-

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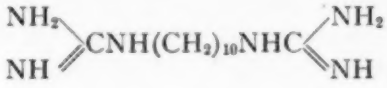
somiasis animals often showed hypoglycemia, a fact which pointed further to a relationship between these infections and the availability of glucose to the infecting parasite.

These observations led to a search for a therapeutic agent against trypanosomiasis among hypoglycemia-producing chemicals. Insulin was studied first but was shown to be ineffective. The search then turned to synthalin. As may be seen in the diagram, synthalin consists of an alkyl chain buttressed at either end by a guanidine radical, a carbon atom having all four of its valences attached to hydrogen-carrying nitrogen atoms.



SYNTHALIN

This compound was found to be a potent protozoicidal agent against trypanosomal infections in rats and as little as one part in 200 million killed trypanosomes in cultures. However, the protozoicidal effects of synthalin appeared to have no relation whatsoever to the lowering of blood sugar.

The high degree of toxicity of synthalin in relation to its therapeutic effectiveness stimulated an examination of other compounds of this general type in a search for a potent and less toxic drug. A large number of new compounds were synthesized including alkyl- and alkylene-amines, amides, isethioureas and guanidines. The most effective of these were found to be certain alkyl and aromatic preparations having terminal amidino groups similar to those of the synthalin molecule. Subsequent work has shown that these ammoniacal polar groups are responsible for the therapeutic effects of the series. The central alkyl and aromatic groups serve as carriers for the active amidino terminal radicals, and give the compounds varying physical properties and varying degrees of toxicity.

Especially satisfactory results were obtained in the laboratory treatment of experimental protozoal infections with three compounds: (1) 4:4′-diamidino stilbene, now known as "stilbamidine," (2) 4:4′ diamidinodiphenoxy pentane now known as "pentamidine," and (3) 4:4′ diamidinodiphenoxy propane now known as "propamidine." These compounds appeared to possess a species rather than a class specificity against trypanosomes as *T. rhodesiense* and *T. congolense* infections were shown to be helped whereas *T. cruzi* infections were not.[22] Further studies showed that animals infected with babesiasis or leishmaniasis could be cured, but certain spirochetal infections were not affected.

Thus, an attempt to find a cure for trypanosomal infections among blood sugar lowering compounds had resulted in the discovery of effective chemotherapeutic compounds whose protozoicidal powers did not seem to be related to the ability to lower blood sugar. What is more, these compounds were also found to have therapeutic value in leishmaniasis of animals [4] so that

therapeutic trials in man were clearly justified. These are now in progress, and the results published thus far are summarized below.

Pharmacology of Diamidines

Toxicity in Laboratory Animals. A study of the toxic properties of diamidines showed that these drugs were well tolerated by mice even when they were administered in relatively large amounts,[35] whereas therapeutic activity was present even with extraordinarily small doses. These animals tolerated doses up to one milligram to 20 grams of body weight, whereas as little as 0.005 to 0.00625 milligram to 20 grams of body weight would suffice to clear the peripheral blood of Babesial parasites in more than 50 per cent of infected animals tested. Doses of 2 mg. per 20 gram mouse were almost invariably fatal, the animals showing narcosis, dyspnea, tremors and convulsions within a few minutes after the injection. Death generally ensued in about one hour. Fractional doses of 0.1 mg. per 20 gram animal could be given daily for long periods without producing signs of intoxication.

In rabbits, the maximum tolerated dose of stilbamidine or pentamidine given by the intravenous route was 20 mg. per kg. In cats and dogs, doses of 5 to 10 mg. per kilogram were generally followed by a marked fall in blood pressure, but the animals recovered within a few minutes.

Devine [10] found that successive small doses of diamidines were generally well tolerated, but nitrogen retention was evident after doses of 15 mg. per kilogram in rabbits. Higher doses produced hyperglycemia of short duration as well as nitrogen retention. No significant evidence of hepatic damage could be demonstrated other than the hyperglycemia which was considered to be a possible sign of hepatic toxicity.

In cattle, Daubney and Hudson [8] found that doses of pentamidine large enough to cause death produced edema of the gastric mucosa, fatty degeneration of the liver, petechiae in the endocardium and epicardium and congestion of the meningeal vessels. These authors noted that cattle tolerate stilbamidine in doses at least four times higher than the fatal dose of pentamidine.

Toxicity in Man. The earliest trials of diamidines in man showed that administration of doses exceeding 1.0 mg. per kilogram of body weight would provoke flushing of the face, epigastric discomfort, headache, a rapid pulse, sweating, retching and occasionally vomiting in some patients. However, these symptoms passed within half an hour and often failed to reappear after the second or third injection.

Napier and Sen Gupta [28] and Sen Gupta [31] reported that among 100 patients with leishmaniasis treated with 4:4′ diamidino-diphenyl-ethylene, four a few months after injection had developed numbness and partial anesthesia of the forehead but no evidence of any other neurologic disturbance. They concluded that these symptoms had been caused by a toxic degenerative lesion of the pons, and noted also that this toxic reaction tended

to improve spontaneously with the passage of time. Later Sen Gupta [81] reported a similar reaction in 10 additional cases following stilbamidine therapy.

Solutions of unsaturated diamidines should be freshly prepared before use or kept away from light according to Fulton and Yorke,[13] who reported in 1942 that solutions of stilbamidine increase in toxicity on exposure to sunlight.

Although these drugs appear to be relatively safe, Henry and Grindley [18] reported that in Sudan, treatment of leishmaniasis with both antimonials and stilbamidine resulted in some fatalities. Although they did not report details of their cases they stated that occasional fatalities had occurred either during treatment or shortly after termination of treatment when the patient was considered cured of kala-azar. Sometimes death was said to have occurred after a latent period of some weeks, suggesting a cumulative toxic reaction. No other similar reports of fatal reactions during therapy for leishmaniasis had appeared to the time of writing of this review, and the significance of these observations is uncertain as authorities on kala-azar have repeatedly reported the occurrence of sudden and unexpected deaths in patients with this disease.

The case report of a patient whose death occurred during therapy with pentamidine for trypanosomiasis has recently been published by McComas and Martin [24] but this observation must also be interpreted cautiously in this serious and often fatal disease.

Distribution of Diamidines in the Body. Very little information is available regarding this matter, as no method has been found for the quantitative estimation of these compounds. In 1941 Hawking and Smiles [17] reported stilbamidine solutions exposed to ultra violet light fluoresced brightly even in dilutions of 1/100 to 1/1000 million. Utilizing this observation, the authors found that stilbamidine could be demonstrated in the cells of the liver, kidney, small intestine, skin, hair and vas deferens of the injected mouse. Particularly strong concentrations were noted in the granules of the trypanosomes, suggesting that the drug had a particular affinity for these parasites. They found that stilbamidine was excreted in the urine in high concentrations during the first seven hours after administration, but after two days the amount excreted was extremely small. None was excreted in the bile. The presence of blood in an organ was reported to mask this fluorescence.

By using this same technic Henry and Grindley [18] showed that 10 per cent of stilbamidine injected intravenously was excreted in the urine within two and one-half days following the injection.

Clinical Trials

Diamidines in Treatment of Leishmaniasis. Both stilbamidine and pentamidine have been given to patients with leishmaniasis with favorable

results. The effectiveness of stilbamidine, however, appears to be somewhat greater than that of pentamidine. An analysis of the reported studies of the treatment of patients with this disease is recorded in table 1.

Diamidines in Treatment of Trypanosomiasis. The effectiveness of the diamidines in treatment of human trypanosomiasis cannot yet be finally assessed. The reports published thus far indicate that these drugs are notably effective for patients with the disease in its early phases but less potent in the later stages. Table 2 presents a summary of the published reports of these clinical studies.

TABLE I

Clinical Trials of Diamidines in Leishmaniasis

Author	Disease Treated	No. of Cases	Drug Used	Results
Adams and Yorke,[2,3] 1939, 1940	Indian Kala-azar	2	Stilbamidine	Immediate cures
Adler and Rachmilewitz,[5] 1939	Leishmania Infantum	1	Stilbamidine	Immediate cure
Napier and Sen Gupta,[27,31] 1940, 1943	Indian Kala-azar	104	Stilbamidine	98% Immediate cures
Kirk and Sati,[20] 1940	Sudan Kala-azar	28	Stilbamidine	Immediate cures 23 Improved 3 Died 2
Wingfield,[34] 1941	Indian Kala-azar	1	Stilbamidine	Immediate cure
Adams,[1] 1941	Indian Kala-azar	1	Pentamidine	Immediate cure
Humphreys,[19] 1942	Oral Pharyngeal Leishmaniasis	1	Pentamidine	Immediate cure
Somers,[30] 1944	Sudan Kala-azar	5	Stilbamidine	Immediate cures 4 Relapse 1

Prophylactic Use of Diamidines against Trypanosomiasis. In 1944 Van Hoof, Henrard and Peel [33] reported that pentamidine is effective as a prophylactic agent against trypanosomiasis. Two volunteers injected with a single dose of 0.002 gm. or 0.003 gm. per kilogram of body weight subsequently resisted for 10 to 20 months repeated bites of infective tsetse flies. No case of sleeping sickness was found among natives of a heavily infected trypanosomiasis focus of the Kwango district in Belgian Congo, after they were given 0.002 to 0.003 gm. per kilogram of pentamidine, whereas new infections were discovered in 2.5 per cent of a series of natives used as controls.

Diamidines in Treatment of Other Protozoal Infections. Daubney and Hudson [9] have reported that stilbamidine is "remarkably effective" in the

treatment of *Babesia canis* infections of dogs, and also noted cures in two instances of *Babesia cabelli* infections (biliary fever) in horses. The observations of Daubney and Hudson were confirmed by Carmichael [7] who treated 116 dogs infected with babesiasis (tick fever) and concluded that propamidine was the most valuable drug available for this disease. Of their animals 102 were cured with a single dose; 10 relapsed, but were cured with a second dose. Only four of the animals died. Fulton [12] has reported that

TABLE II

Clinical Trials in Diamidines in Trypanosomiasis

Author	Disease Treated	No. of Cases	Drug Used	Results
Harding,[16] 1940	Nigerian Trypanosomiasis	13	Stilbamidine	Cured 3 Improved 1 Unchanged 1 Worse 8
McLetchie,[26] 1940	Nigerian Trypanosomiasis	14	Stilbamidine	Cured 8 Improved 4 Died 2
Bowesman,[6] 1940	Trypanosomiasis	34	Stilbamidine	Improved 28 Unimproved 2 Died 4
Saunders,[29] 1941	Trypanosomiasis	14	Pentamidine	Cured 11 Improved 3
Lawson,[21] 1942	Gambian Trypanosomiasis	53	Pentamidine	Cured 41 Improved 7 Unimproved 4 Died 1
Gilbert,[14] 1943	Trypanosomiasis	14	Pentamidine	Improved 11 Unimproved 1 Died 2

stilbamidine is definitely anti-malarial in cases of *Plasmodium relictum* infections of canaries and against *Plasmodium knowlesi* infections of monkeys.

BACTERICIDAL EFFECTS OF DIAMIDINES

Experimental Studies. In 1942 Fuller [11] reported that Gram-positive cocci are killed when exposed to diamidines and noted that the *Streptococcus viridans* is the most sensitive and *Staphylococcus aureus* the least sensitive member of this group. Gram-positive anaerobic bacilli are more resistant than the cocci but more sensitive than Gram-negative bacilli. Of the anaerobes, *Clostridium oedematiens* is most sensitive and *Clostridium welchii* least sensitive. This order of sensitivity of bacteria to diamidines is similar to their sensitivity to sulfonamides.

As a result of these observations, Thrower and Valentine [32] carried out in vitro experiments using *Staphylococcus aureus* to test the bacteriostatic properties of propamidine, and reported that against certain strains of

staphylococcus, propamidine was more effective than sulfathiazole. He noted also that the antibacterial effect of the amidines was not inhibited by p-aminobenzoic acid which antagonizes the action of the sulfonamides.

In a typical experiment, sulfathiazole exerted an antibacterial effect in a minimal effective concentration of 1:32,000, whereas propamidine was found to be effective in a minimal concentration of 1: 125,000. Preliminary studies showed that against clostridia, propamidine exerted an effect of the same order as against staphylococci.

Antibacterial Effects of Diamidines in Plastic Surgery and in Open Wounds. In the field of plastic surgery, persisting streptococcal infections have not infrequently delayed healing of wounds and have provided a source for cross-infections in wards. These streptococcal infections have been in some instances most difficult to control. In consideration of the antibacterial properties of diamidines as detailed above, Thrower and Valentine [32] studied the effects of using propamidine in a jelly base as a dressing for such infected wounds, and reported that under such circumstances this drug was remarkably effective. Wounds which had remained infected for more than a year showed rapid improvement, permitting early skin-grafting or promoting early spontaneous healing. McIndoe and Tilley [25] found that 0.1 per cent propamidine in a water-soluble jelly base successfully eradicated similar infections. These workers were particularly impressed by a lack of irritation of the surrounding skin following this treatment. Not all staphylococcal infections were cleared, however, and *B. proteus,* Pseudomonas, and *B. subtilis* infections also remained unaffected.

Morley and Bentley [23] reported that propamidine in a soft cream combined with a local anesthetic, controlled streptococcal and staphylococcal infections of burned surfaces. These authors, like McIndoe and Tilley, noted the failure of this drug to control pus producing saprophytes such as *B. proteus,* Pseudomonas and *B. subtilis.*

Similar results were observed by Hall and Gross [15] in the treatment of ulcers of the leg, deep infected wounds, and infected burns.

Therapeutic Trial of Diamidines in Rheumatoid Arthritis

Although the cause of rheumatoid arthritis remains unknown, a considerable amount of indirect evidence suggests that an infectious agent may be responsible. Since present-day methods of treatment for rheumatoid arthritis are admittedly insufficient, the discovery of a new group of antibacterial chemotherapeutic agents was believed to warrant their trial in patients with this condition.

Because of these considerations, six soldiers suffering with active and progressive rheumatoid arthritis were given a trial of therapy with diamidine derivatives. Four were treated with stilbamidine and two with propamidine. The patients were all males whose ages ranged from 21 to 54 years. The

arthritis had been present for periods ranging from six months to eight years. In all of these patients the disease had appeared insidiously. Each had a polyarticular inflammation which had run a progressive course, and in each patient the progress of the inflammation of joints was continuing. Each patient was crippled to some extent by his articular disease, and the changes which had taken place in the joints were easily detectable on clinical examination. Many of the involved joints had a spindle shaped appearance because of swelling of the joints accompanied by atrophy of the adjacent muscles. Periarticular and synovial thickening were common, and effusions were present in some joints. The roentgenograms showed normal findings where the involvement of joints was recent in onset and in the further advanced stages of the disease showed narrowing of joint spaces, atrophy of epiphyseal bone and in one far advanced instance, marginal lipping.

These six patients manifested more or less severe degrees of systemic disturbances such as loss of weight, some degree of hypochromic anemia and elevation of the erythrocyte sedimentation rate.

The joints were carefully examined before beginning the therapy and the findings of the examiners were filed. At the termination of the courses of therapy each patient was carefully reëxamined in regard to the character of the disease in each affected joint. The findings at the beginning and at the end of the therapeutic program were then compared.

Dosage. The diamidines were prepared by solution in buffered, slightly alkaline distilled water. The concentration of the solution was such that each cubic centimeter contained 5 mg. of the drug. Each patient was given two preliminary doses of 5 c.c. (25 mg.) intramuscularly at intervals of three or four days. When it was observed that these intramuscular amounts were well tolerated, the patients were given the drug in doses of 10 c.c. (50 mg.) intravenously on Monday, Wednesday and Friday of each week. The intravenous injections were given slowly; approximately five minutes were required for intravenous injection of 10 c.c. of the solution. Injections were continued until each patient had received a total of one gram of the drug.

Laboratory Studies. The level of hemoglobin, erythrocyte count, leukocyte counts, urinalysis and erythrocyte sedimentation rates were determined at frequent intervals.

Results. The patients did not appear to be benefited in any way. There was no lessening of the degree of swelling or tenderness and no significant alteration in the sedimentation rate, level of hemoglobin or erythrocyte count. Of six patients treated, five stated that they had experienced some degree of subjective improvement of appetite. However, there was no significant gain in body weight.

No toxic reactions were observed. None of the tests disclosed any significant alteration from the findings which were noted before the administration of the drug.

After administering these drugs for 30 days, and again at the completion

TABLE III

Summary of Clinical Data in Patients with Rheumatoid Arthritis Treated by Diamidines

Case No.	Age	Duration Arthritis Years	Clinical Observations Regarding Joints	Report of Roentgenograms	Hb. R.B.C. Sed. Rate	Activity of Arthritis	Amount of Diamidine and Manner of Administration
1	54	8	Shoulders limited in abduction to 90°. Atrophy of muscles about shoulders. Right elbow swollen and held in 35° flexion. Right wrist swollen and tender. Left elbow swollen and held in 50° flexion. Left wrist swollen, tender and limited in motion. Heads of all metatarsal bones prolapsed.	*Rt. Elbow:* Proliferation of bone at medial aspect of humero-ulnar joint. Decalcification of bones about elbow joint.	*Hb.* 12.5 gm. *R.B.C.* 4.05 mil. *Sed. Rate* 40 mm./hr.	Severe	July 31, Aug. 3, 1944, 25 mg., I.M. Aug. 5 to Sept. 25, 1944, 50 mg. I.V., 3x weekly Total Stilbamidine 1250 mg.
2	21	6/12	Right sternoclavicular joint swollen and tender. Right elbow swollen and tender, painful on motion. Knees swollen and contained excess fluid.	*Rt. Knee:* Negative	*Hb.* 15 gm. *R.B.C.* 5.28 mil. *Sed. Rate* 29 mm./hr.	Moder-ate	June 16 to Sept. 1, 1944, 50 mg. Stilbamidine, I.V. 3x weekly Total 1000 mg.
3	22	9/12	Wrists swollen, tender and painful on motion. Knees swollen, contained excess fluid and painful on motion.	*Knees:* Negative	*Hb.* 15 gm. *R.B.C.* 4.9 mil. *Sed. Rate* 7 mm./hr.	Severe	June 15 to Sept. 1, 1944, 50 mg. Stilbamidine, I.V. 3x weekly Total 1000 mg.

TABLE III—*Continued*

Case No.	Age	Duration Arthritis Years	Clinical Observations Regarding Joints	Report of Roentgenograms	Hb. R.B.C. Sed. Rate	Activity of Arthritis	Amount of Diamidine and Manner of Administration
4	35	2	Right elbow swollen, tender and held in 75° flexion and in 105° extension, painful on forced motion. Left elbow swollen, tender, painful on motion and limited in flexion. Proximal interphalangeal joint third finger of right hand swollen and tender. Right knee moderately swollen with excess fluid. Left knee swollen, tender on motion and limited in flexion. Many other joints similarly affected.	*Ankles:* Negative	*Hb.* 9 gm. *R.B.C.* 3.5 mil. *Sed. Rate* 30 mm./hr.	Severe	June 15 to Sept. 1, 1944, 50 mg. Propamidine, I.V. 3x weekly Total 1000 mg.
5	28	10/12	Elbows swollen and tender. Right knee swollen and contained excess fluid.	*Rt. Elbow:* Negative	*Hb.* 12.5 gm. *R.B.C.* 4.3 mil. *Sed. Rate* 15 mm./hr.	Severe	June 15 to Aug. 15, 1944, 50 mg. Propamidine, I.V. 3x weekly Total 1000 mg.
6	38	5	Right elbow held in 30° flexion with thickening of synovial membrane. Left elbow swollen and held in 15° flexion. Wrists limited in motion. Proximal interphalangeal joint right second finger swollen, discolored and tender. Metacarpophalangeal joint No. 1 left and interphalangeal joint No. 1 left, swollen, discolored and tender. Metacarpophalangeal joints No. 2 and No. 3 left and the proximal interphalangeal joint No. 3 left, swollen, tender. Quadriceps extensor muscles atrophied. Knees swollen. Right ankle swollen, and tender, and right subastragalar joint limited in motion. Mouth opening limited to 2 cm.	Severe destructive changes involving many joints.	*Hb.* 10 gm. *R.B.C.* 4.3 mil. *Sed. Rate* 52 mm./hr.	Severe	June 15 to Aug. 15, 1944, 50 mg. Stillbamidine, I.V. 3x weekly Total 1000 mg.

TABLE IV

Infections Controllable by Diamidines

Disease	Synonyms	Causative Organism	Animal Affected
Leishmaniasis	Kala-azar Tropical Splenomegaly Dum Dum Fever	*Leishmania donovani*	Man
Trypanosomiasis	African Sleeping Sickness	*Trypanosoma rhodesiense* *gambiense*	Man
Babesiasis	Tick Fever	*Babesia canis*	Dogs
	Biliary Fever	*Babesia cabelli*	Horses
Malaria	—	*Plasmodium relictum*	Canary
	—	*Plasmodium knowlesi*	Monkey
Wound Infections	—	Streptococci Staphylococci	Man

of the course, renal and hepatic functions were studied by means of phenolsulfonphthalein tests, and urea clearance tests for renal function, and bromsulfalein test for liver function. These tests remained normal.

SUMMARY

1. A group of chemical substances consisting of various organic radicals carrying strongly basic amidino groups have been found to be of considerable therapeutic value in the treatment of a number of protozoal and bacterial diseases.

2. These compounds appear to be particularly powerful in their action against human leishmaniasis, a common and exceedingly dangerous disease of the tropics.

3. Less certain but very promising effects have been reported in treatment of human trypanosomiasis.

4. Notable therapeutic value has been demonstrated for these compounds in the treatment of infections of surface wounds such as in burned surfaces, and in wounds associated with plastic surgery.

5. Control of protozoan infestations of dogs and horses with organisms belonging to the genera of Babesia, and of malaria in canaries and monkeys has been achieved with these drugs.

6. Patients with rheumatoid arthritis who were submitted to preliminary trials of therapy with diamidines showed no tendency to improvement.

BIBLIOGRAPHY

1. ADAMS, A. R. D.: Studies in chemotherapy. XXVI. A case of Indian kala-azar treated with 4:4′ diamidinodiphenoxy pentane, Ann. Trop. Med., 1941, xxxv, 53.

2. Adams, A. R. D., and Yorke, W.: Studies in chemotherapy. XXIII. A case of Indian kala-azar treated with 4:4′ diamidino stilbene, Ann. Trop. Med., 1939, xxxiii, 323.
3. Adams, A. R. D., and Yorke, W.: Studies in chemotherapy. XXV. A second case of Indian kala-azar treated with 4:4′ diamidino stilbene, Ann. Trop. Med., 1940, xxxiv, 173.
4. Adler, S., and Tchernomoretz, I.: The action of 4:4′ diamidino stilbene on *Leishmania donovani* in the Syrian hamster, *Circetus auratus*, Ann. Trop. Med., 1939, xxxiii, 313.
5. Adler, S., and Rachmilewitz, M.: A note on the treatment of a case of *Leishmania infantum* with 4:4′ diamidino stilbene, Ann. Trop. Med., 1939, xxxiii, 327.
6. Bowesman, C.: A short report on the use of 4:4′ diamidino stilbene in the treatment of human sleeping sickness, Ann. Trop. Med., 1940, xxxiv, 217.
7. Carmichael, J.: Treatment of canine babesiasis by 4:4′ diamidino diphenoxy propane, Ann. Trop. Med. and Hyg., 1941, xxxv, 191.
8. Daubney, R., and Hudson, J. R.: Action of two aromatic diamidines on *Trypanosoma congolense* infections in cattle with a note on delayed poisoning by 4:4′ diamidino diphenoxy pentane, Ann. Trop. Med., 1941, xxxv, 175.
9. Daubney, R., and Hudson, J. R.: A note on the chemotherapeutic action of 4:4′ diamidino stilbene in *Babesia canis* infections of domestic animals, Ann. Trop. Med. and Hyg., 1941, xxxv, 187.
10. Devine, J.: Studies in chemotherapy; changes in the blood produced by administration of 4:4′ diamidino stilbene, Ann. Trop. Med., 1940, xxxiv, 67.
11. Fuller, A. T.: Antibacterial actions and chemical constitution in long chain aliphatic bases, Biochem. Jr., 1942, xxxvi, 548.
12. Fulton, J. D.: The course of *Plasmodium relictum* infection in canaries and the treatment of bird and monkey malaria with synthetic bases, Ann. Trop. Med., 1940, xxxiv, 53.
13. Fulton, J. D., and Yorke, W.: Increased toxicity of old solutions of stilbamidine, Ann. Trop. Med., 1942, xxxvi, 134.
14. Gilbert, S. W.: Pentamidine in treatment of late cases of sleeping sickness, Trans. Roy. Soc. Trop. Med. and Hyg., 1943, xxxvi, 353.
15. Hall, M. H., and Gross, Clara D.: Propamidine at an E. M. S. Hospital, Lancet, 1943, i, 140.
16. Harding, R. D.: A trial with 4:4′ diamidino stilbene in the treatment of sleeping sickness at Gadau, Northern Nigeria, Ann. Trop. Med., 1940, xxxiv, 101.
17. Hawking, F., and Smiles, J.: The distribution of 4:4′ diamidino stilbene in trypanosomes and mice as shown by fluorescence, Ann. Trop. Med., 1941, xxxv, 45.
18. Henry, A. J., and Grindley, D. N.: Fluorescence and absorption of stilbamidine and its estimation in biological fluids, Ann. Trop. Med., 1942, xxxvi, 102.
19. Humphreys, R. M.: Two cases of oral pharyngeal leishmaniasis treated with pentamidine, Ann. Trop. Med., 1942, xxxvi, 9.
20. Kirk, R., and Sati, M. G.: Notes on some cases of Sudan kala-azar treated with 4:4′ diamidino stilbene, Ann. Trop. Med., 1940, xxxiv, 83.
21. Lawson, T. L.: Trypanosomiasis treated with "pentamidine," Lancet, 1942, ii, 480.
22. Lourie, E. M., and Yorke, W.: Studies on chemotherapy. XXI. The trypanocidal action of certain aromatic diamidines, Ann. Trop. Med., 1939, xxxiii, 289.
23. Morley, George H., and Bentley, J. P.: Propamidine in burns, Lancet, 1943, i, 138.
24. McComas, G., and Martin, N. H.: Trypanosomiasis treated with pentamidine: A fatal case, Lancet, 1944, i, 338.
25. McIndoe, A. H., and Tilley, A. R.: Propamidine in chronic streptococcal infection of raw surfaces, Lancet, 1943, i, 136.
26. McLetchie, J. L.: The treatment of early cases of Nigerian trypanosomiasis with 4:4′ diamidino stilbene, Ann. Trop. Med., 1940, xxxiv, 217.

27. Napier, L. E., and Sen Gupta, P. C.: Diamidino stilbene in the treatment of kala-azar, Ann. Trop. Med. and Hyg., 1941, xliv, 45.
28. Napier, L. E., and Sen Gupta, P. C.: A peculiar neurological sequel to administration of 4:4′ diamidino diphenyl ethylene (M & B 744), Indian Med. Gaz., 1942, lxxvii, 71.
29. Saunders, G. F. T.: Preliminary report on the treatment of sleeping sickness by 4:4′ diamidino diphenoxy pentane, Ann. Trop. Med., 1941, xxxv, 169.
30. Somers, R. B.: Kala-azar treated with 4:4′ diamidino stilbene, Lancet, 1944, i, 531.
31. Sen Gupta, P. C.: Observations on the neuropathic sequel of diamidino-stilbene therapy in kala-azar, Indian Med. Gaz., 1943, lxxviii, 537.
32. Thrower, W. R., and Valentine, F. C. O.: Propamidine in chronic wound sepsis, Lancet, 1943, i, 133.
33. Van Hoof, L., Henrard, C., and Peel, E.: Pentamidine in prevention and treatment of trypanosomiasis, Trans. Roy. Soc. Trop. Med. and Hyg., 1944, xxxvii, 271.
34. Wingfield, A. L.: 4:4′ diamidino stilbene in the treatment of kala-azar, Ann. Trop. Med., 1941, xxxv, 55.
35. Yorke, W.: Recent work on the chemotherapy of protozoal infections, Trans. Roy. Soc. Trop. Med. and Hyg., 1940, xxxiii, 463.

CASE REPORTS

PNEUMOCOCCIC ARTHRITIS: REPORT OF A CASE TREATED WITH PENICILLIN*

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Recently Boger [1] reported a case of "primary" or "cryptogenic" pneumococcic arthritis cured with sulfadiazine orally and intra-articularly. Boger reviewed the literature and collected 227 cases of pneumococcic arthritis of which 34 were considered "primary." Of these, only four cases were adequately described and can be definitely called "primary" pneumococcic arthritis. We are reporting a case of "primary" pneumococcic arthritis treated with penicillin.

Case Report

C. D., a negro laborer, aged 29, was admitted to the Gallinger Municipal Hospital on January 5, 1944, with the complaint of pain and swelling of the left knee for five days. At that time, upon stepping out of bed, he fell to the floor. He found his left knee was swollen, hot, painful, and unable to bear weight. These symptoms persisted until the time of admission. Two months previously he had struck his right leg with a pick. He was treated at a clinic and was told the bone appeared splintered on the roentgenogram, but only local dressings were applied. This leg remained painful, and weight-bearing was slightly difficult. However, he continued to work until the onset of his present illness. The remainder of his history was negative.

Examination revealed the patient to be well developed and nourished. The left knee was greatly swollen, red, painful, and much distended with fluid. It was held in semi-flexion. The periarticular tissues were edematous, white, and shiny, and the inflammation extended up to the upper one-third of the thigh. The venous circulation was prominent. Slight point tenderness was present over a small scar on the anterior surface of the right leg at the junction of the upper and middle thirds. The temperature was 102° F., pulse 80, respiratory rate 22. The remainder of the physical examination was normal.

A hemogram showed a hemoglobin of 77 per cent, red blood cell count of 3.35 millions and 14,450 leukocytes with 80 per cent neutrophiles. Urinalysis was negative. Roentgenograms of the lower extremities revealed marked soft tissue swelling of the left knee with no other abnormalities. Aspiration yielded 90 c.c. of yellow seropurulent material which, on culture, showed Type 12 pneumococci.

The patient was placed on sulfadiazine, 4 grams initially and 1 gram every four hours. Skin traction was applied to the left lower extremity. This therapy was continued for three weeks without clinical improvement, and the cultures from the knee fluid remained positive. In spite of repeated aspirations the knee continued to accumulate large amounts of fluid. The patient's general condition remained good. On the twenty-fourth hospital day, the patient was started on intra-articular penicillin,

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† This study was done prior to Dr. Feffer's entrance into the Armed Forces.

15,000 units daily. These injections were continued for five days without any change in the condition of the knee, although the knee fluid became sterile. Then, 12,500 units were administered twice daily into the joint space. After 10 days of this regime, the knee appeared healed with only slight flexion deformity, which disappeared gradually in a few weeks. The patient returned six months later for an unrelated illness with no evidence of any abnormality of the knee joint.

Comment

The features of pneumococcic arthritis are variable. Only one joint is involved in about 75 per cent of cases. Pain, which is always present, varies greatly in intensity and is sudden or insidious in onset. Periarticular involvement may be slight or extensive, and the suppuration may perforate the capsule and extend through all the surrounding tissues into the musculature. It is generally agreed that "primary" pneumococcic arthritis is a metastatic focus of a bacteremia for which the primary site cannot be demonstrated. Although the diagnosis of pneumococcic arthritis should not be made until the pneumococci have been isolated from the joint fluid, several investigators [2, 3] have reported certain findings which they consider pathognomonic. The periarticular edema is white, the venous collateral circulation prominent, and regional lymphadenopathy is not marked. Joint fluid reaccumulates rapidly after aspiration. The local findings and fever are marked, but the patient's general condition appears good. Our patient demonstrated all these features except that his temperature never exceeded 102° F. Most authors, however, do not believe that there are any symptoms or signs which distinguish pneumococcic from other types of pyogenic arthritis.

Prior to the introduction of chemotherapy and antibiotics, treatment consisted of repeated aspirations, injections of air or irrigation with various antiseptics. Passive movements and physical therapy were used as soon as manipulation was tolerated to prevent wasting of muscles and joint disability. Arthrotomy has generally been abandoned. Immobilization is used only in ankylosing cases. It is difficult to evaluate the effect of treatment since spontaneous recoveries have been reported in three out of the four proved cases of "primary" pneumococcic arthritis. The fourth case reported by Boger recovered on sulfadiazine given orally and intra-articularly. However, sulfadiazine orally was ineffective in our patient. Intra-articular penicillin did effect a cure in 10 days with the use of adequate doses twice daily. Our patient had complete restoration of function. Generally, this has been the experience of other investigators. Disability is usually slight when it does occur.

Summary

A case of "primary" pneumococcic arthritis, cured with intra-articular penicillin is reported. Certain pathognomonic features, previously described, were observed.

BIBLIOGRAPHY

1. Boger, W. P.: Pneumococcic arthritis. Report of case of so-called primary pneumococcic arthritis, Jr. Am. Med. Assoc., 1944, cxxvi, 1062.
2. Plisson and Brousse: Arthrite purulente primitive à pneumocoques du genou chez l'adulte, Lyon chir., 1920, xvii, 705.
3. Chantemesse, Mocaigne and Chipault: Cited by Plisson and Brousse.[2]

SUBENDOCARDIAL MYOCARDIAL INFARCT*

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This is a report of a case of extensive subendocardial myocardial infarction involving the interventricular septum and the anterior wall of the left ventricle. There was no coronary occlusion, and the electrocardiogram showed no evidence suggestive of a recent myocardial infarct. The rarity of this condition warrants a case report.

Case Report

An 82 year old white female‡ was admitted for the first time after she had collapsed following the extraction of two teeth. Diabetes mellitus was diagnosed at that time, and the Wassermann and Kahn reactions were found to be positive (4 plus). After six days of treatment with insulin and diet the patient was discharged with the diabetes improved. About one year later she was re-admitted following an injury to the left foot complicated by dry gangrene of the fourth left toe. During her stay at home the patient had not taken any insulin, and she had followed her diet inadequately. The family history disclosed that one brother died at the age of 69 of coronary thrombosis. She was gravida VI, para II, with three premature births and one stillbirth, and two live children. On admission her chief complaints were pain and swelling of the left foot and some frequency in urination, urgency and incontinence without dysuria. Physical examination revealed a well-developed, well-nourished white woman, resting comfortably in bed. The temperature was 98.6° F., the pulse was 88 per minute, the rhythm was regular. Respirations were 20 per minute, arterial blood pressure was 168 mm. Hg systolic and 70 mm. diastolic. The heart was enlarged to the left, reaching the anterior axillary line in the fifth intercostal space. A high pitched systolic murmur was heard at the apex and the aortic second sound was louder than the pulmonic. The fourth toe of the left foot was bluish-black, and there was reddening and swelling of the dorsum of the foot. The pulse of the left dorsalis pedis artery was not palpable. The clinical diagnosis was gangrene of the left fourth toe and generalized arteriosclerosis. The hemoglobin was 10.4 gm., the erythrocyte count was 4,660,000 per cubic mm. and the leukocytes were 14,300 per cubic mm. with a normal differential count. The fasting blood sugar was 250 mg. per cent, and the non-protein nitrogen was 40 mg. per cent. Twenty-four hour catheterized urine specimen showed an acid reaction, specific gravity 1.013, sugar and tests for acetone were negative. The sediment showed three to five white cells. Roentgenogram of the left foot revealed a fracture to the base of the fifth metatarsus.

The patient was placed on a diabetic diet, received acetylsalicylic acid and sulfadiazine (gm. 1, every 4 hours). Local heat and moist application produced some local improvement.

The temperature ranged between 98.6° and 100° F., and her general condition was good for five days when the temperature rose to 101° F. without elevation of the respiratory or pulse rate. Twenty-four hours later, on the sixth night after admission, the patient suddenly became very restless, had an emesis and an involuntary bowel

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‡ For the use of the clinical record we are indebted to Dr. M. D. Allweiss.

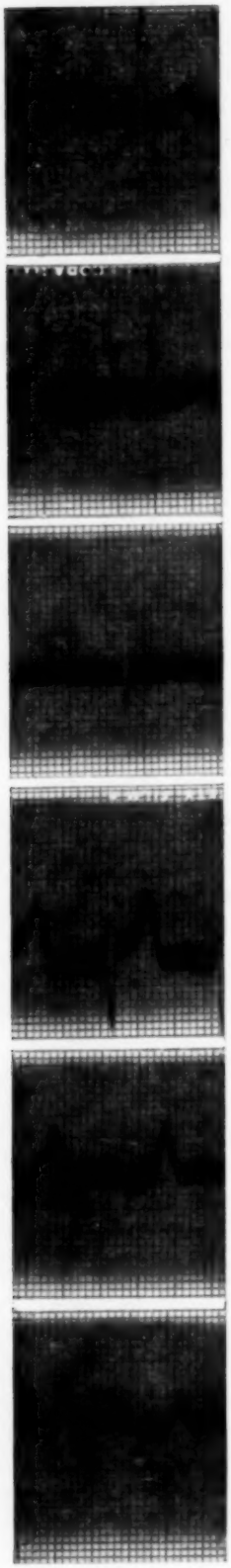

FIG. 1.

movement. She developed marked dyspnea, râles were heard over the lungs and mucus accumulated in her throat. The blood pressure at the beginning of this episode was 116 mm. Hg systolic and 60 mm. diastolic and slowly dropped to 100 mm. Hg systolic and 60 mm. diastolic. The pulse was of fairly good quality and regular, with a rate of 100 to 110. The patient vomited twice more. The impression was that this attack was caused by an acute coronary occlusion. The possibility of a pulmonary embolus was also considered. Oxygen, aminophyllin and morphine sulfate were administered, and the patient improved. Urine examination at that time revealed 4 plus sugar but no acetone; the vomitus showed a 4 plus occult blood. The electrocardiogram taken 17 hours after the beginning of the attack disclosed a definitely abnormal curve with left ventricular preponderance, and no evidence of a recent myocardial infarct. The patient was comfortable and in good condition for 36 hours following the attack, then suddenly she started to gasp for breath, became pale and

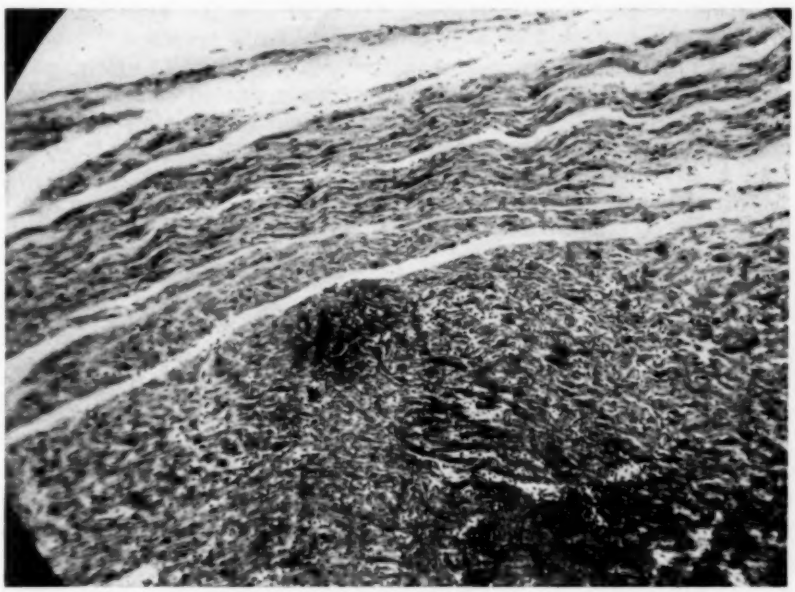

FIG. 2. Subendocardial myocardial infarct. Note the recent infarct and the narrow rim of normal myocardium immediately adjacent to the endocardium.

unconscious. The pulse became weak and rapid, the skin cold and clammy and the patient died 10 minutes later.

Necropsy. An autopsy performed six hours after death disclosed the following findings: Severe generalized arteriosclerosis, nephrosclerosis of the arteriolar variety, moderate hypertrophy of the heart, severe coronary arteriosclerosis with narrowing of branches of the left coronary artery in many places, a recent subendocardial myocardial infarct of the left ventricular wall, edema and hyperemia of the lungs, bilateral hydrothorax, chronic passive hyperemia of liver and spleen, moderate fibrosis of the pancreas, multiple myofibromata of the uterus, multiple minute adenomata of the kidneys and early "cytotoxic" contraction of the suprarenals. There was no gross or microscopic evidence of lesions attributable to syphilis.

The gross description of the heart was as follows: The heart was moderately enlarged, especially in its left portion, and weighed 400 gm. The subepicardial fat

was normal. The chambers and endocardium were normal. The tricuspid, pulmonic, aortic and mitral rings measured respectively: 10.0, 7.2, 7.0, and 8.0 cm. in circumference. The tricuspid and mitral leaflets and the aortic cusps exhibited a slight sclerotic thickening. Within the base of the aortic and the mitral rings were a few calcific areas which extended to the septum membranaceum. The myocardium was red-brown. The right ventricular wall measured up to 0.4 cm., and the left up to 1.7 cm. in thickness. The upper portion of the interventricular septum presented a soft, yellowish-red area on its left ventricular aspect. On section, numerous subendocardial hemorrhages and yellowish brown areas were noted throughout the septum extending into the anterior wall of the left ventricle and into the anterior papillary muscle. The coronary ostia were narrowed by calcific aortic plaques. The right ostium was abnormally low and covered by the aortic cusp. The arteries had a normal distribution. The left one presented a very severe sclerosis and atheromatosis throughout with a marked narrowing of the lumen of its various branches at several points. The right coronary artery showed much less severe sclerosis. Neither recent nor old occlusions were noted in the main branches. The aorta was rigid, calcified throughout.

The microscopic examination of the myocardium showed in the interventricular septum many large areas adjacent to the endocardium of the left ventricle in which the muscle fibers had a smudgy appearance and stained very poorly. Between the muscle fibers were numerous polymorphonuclear leukocytes and lymphocytes and some extravasated red blood corpuscles. The separation between the infarcted and normal muscle was clear cut (figure 2). Areas of recent infarction were also seen in the anterior wall of the left ventricle and in the left anterior papillary muscle.

The infarct was judged to be between 24 and 36 hours old.[1] The remaining myocardium exhibited a moderate degree of interstitial fibrosis and some thickening of the wall of the arteries.

Discussion

This case is interesting because of the presence of an extensive subendocardial infarct involving about two-fifths of the thickness of the left ventricular wall without any recent or old occlusion of the coronary arteries, although the mouths of both coronary arteries were narrowed and the branches of the coronary arteries were sclerotic, of the "pipe-stem" type, presenting numerous narrowings. Physiologically, therefore, there was doubtlessly chronic coronary insufficiency. This insufficiency was probably increased by the presence of arteriosclerotic plaques in the aorta at the mouths of the coronary arteries. A moderate degree of interstitial fibrosis of the myocardium was the only evidence of this chronic coronary insufficiency which must have been present for a number of years. On this basis, and in connection with the presence of an infectious process, the patient developed left heart failure. This, in time, caused slowing of the circulation for which the severely diseased coronary arteries could not compensate and precipitated acute ischemia of the myocardium leading to infarction. Anatomically, this was an extensive confluent subendocardial infarction. The myocardium did not present the picture of focal necrosis which has been frequently described in cases of chronic coronary insufficiency.

In this instance the clinical picture, aside from the absence of pain, was characteristic of myocardial infarct. The electrocardiogram was definitely abnormal, showing a left ventricular preponderance pattern but no changes characteristic of infarct (figure 1).

It is now recognized that concordant S–T elevation in the limb leads or at least the absence of discordant S–T depression is typical of pericarditis due to the involvement of the subepicardial myocardium. Recently the reverse has been suggested as a sign of subendocardial infarction; viz. concordant S–T depression in the limb leads, at least the absence of discordant S–T elevation.[2] On this basis the possibility of a subendocardial infarction might have been considered in this case. The S–T depression in Leads I and II can be considered as indicative of the subendocardial infarction found at necropsy. However, the pattern in this case is not convincing because it might have been produced by left heart strain.

It is amazing that so extensive an infarction could occur in this patient without closure of the artery supplying the area. More interesting is the fact that with so extensive an infarct only the inner layer of the myocardium of the left ventricle was involved. The blood flow on the inner side of the left ventricle is closer to the critical level at which infarction occurs than that of the outer side. This lends support to the concept that during systole the extravascular compression of the coronary vessels increases from the epicardial to the endocardial aspect.[3] The threshold for infarction would therefore be reached with less diminution in coronary flow on the inner aspect.

The most common sites of subendocardial infarcts are the interventricular septum and the papillary muscles of the left ventricle. These areas are farthest away from large coronary branches. A large septal branch was observed by Schlesinger only in a small percentage of human hearts.[4, 5] A second factor is the particular exposure of these regions to intraventricular pressure.

Since the exacerbation of the coronary insufficiency was due to failure of the heart, it is possible that therapy directed to improve the failure might have prevented the fatal outcome. Digitalis is a drug which might have accomplished this.

Summary

A case of extensive subendocardial septal myocardial infarction, occurring without occlusion of the coronary arteries, is presented.

The pathogenesis of this unusual condition and the rationale of therapy are briefly discussed.

The authors are indebted to Drs. O. Saphir and L. N. Katz for their advice.

BIBLIOGRAPHY

1. Mallory, G. K., White, P. D., and Salcedo-Salgar, J.: The speed of healing of myocardial infarction, Am. Heart Jr., 1939, xviii, 647–672.
2. Langendorf, R., and Kovitz, B.: Acute myocardial infarction without deviation of the S–T segment of the electrocardiogram, Am. Jr. Med. Sci., 1942, cciv, 239–246.
3. Johnson, R. J., and DiPalma, J. R.: Intramyocardial pressure and its relation to aortic blood pressure, Am. Jr. Physiol., 1939, cxxv, 234–243.
4. Schlesinger, M. J., and Zoll, P. M.: Incidence and localization of coronary artery occlusion, Arch. Path., 1941, xxxii, 178–188.
5. Blumgart, H. L., Gilligan, D. R., and Schlesinger, M. J.: Experimental studies on the effect of temporary occlusion of coronary arteries. II. The production of myocardial infarction, Am. Heart Jr., 1941, xxii, 374–389.

RUPTURE OF THE SPLEEN DUE TO TULAREMIA: REPORT OF A CASE*

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INTRODUCTION

RUPTURE of the spleen as one of the manifestations or complications of tularemia apparently has rarely if ever before been encountered. A thorough search of the literature reveals no recorded instance of this nature. A patient was recently observed at Vanderbilt University Hospital in whom this condition was found at autopsy following a clinical course in which the exact diagnosis remained obscure. Because of its unusual nature a report of this case seems justified.

CASE REPORT

History. A 41 year old white male farmer was admitted to the medical service of Vanderbilt University Hospital on December 18, 1944 with a chief complaint of abdominal pain of 17 hours' duration.

Throughout the seven years preceding admission he had typical peptic ulcer symptoms which were treated at home by his local physician. Two years before admission he had an episode of massive hematemesis, and was in bed for one month. At this time a duodenal ulcer was demonstrated by roentgen-ray examination. Following this, and until the present illness he had only occasional epigastric distress, which was relieved by alkalies.

Eighteen days prior to admission the patient went rabbit hunting. He killed and dressed several rabbits, none of which appeared sick. Sixteen days before admission he noticed a small "pimple" on the middle finger of the right hand. His wife removed a scab from this lesion, which progressed in size. Fourteen days before admission the patient had pain in the right shoulder, noticed tender "lumps" in the right epitrochlear region and in the right axilla. The same day he had a rather sudden onset of malaise, followed by a shaking chill, high fever, and drenching sweat. At this time, Dr. David Strayhorn of Nashville was consulted, and a diagnosis of tularemia was made. Serum agglutination against *Pasteurella tularensis* at this time was reported as negative. The patient improved somewhat on bed rest and sedation.

The day before admission to the hospital, following a light meal, he developed dull aching non-radiating pain in the epigastric region associated with nausea and a feeling of fullness. Several hours later he was given an enema which was effective. There was no blood or tarry material in the stool. Immediately following the enema, the patient suddenly felt very faint and perspired freely, but did not lose consciousness. His wife noticed that he had become very pale within the space of a few hours. He remained weak, with some fever and profuse sweats, aching epigastric pain, a feeling of fullness, and nausea without vomiting.

The remainder of the history was non-contributory.

Physical examination on admission. His temperature was 97° F., pulse 120, respirations 40, and blood pressure 70 mm. Hg systolic and 40 mm. diastolic.

General appearance: The patient was a well developed, white male lying motion-

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less, appearing acutely ill with narrowed field of consciousness and presenting the picture of peripheral vascular collapse. The skin was extremely pale and covered with beads of clammy perspiration. The pulse was rapid and thready with a blood pressure of 70 mm. Hg systolic and 40 mm. diastolic.

On the dorsal surface of the proximal interphalangeal joint of the right third finger was a red, raised, non-tender encrusted ulcer about 5 mm. in diameter. An enlarged, slightly tender, right epitrochlear node, and two slightly tender, firm, axillary nodes, each about 3 cm. in diameter were palpable. There was no generalized glandular enlargement. The conjunctivae and buccal mucous membrane were extremely pale. The lungs were clear to percussion and auscultation. Examination of the abdomen revealed diffuse tenderness in the epigastrium and moderate upper abdominal distention. There were spasm and rigidity of the recti in the epigastrium. No organs or masses were felt. Peristaltic sounds were diminished.

Laboratory studies on admission. The red blood cell count was 2,440,000. The white blood cell count was 23,900 and the hemoglobin was 8 grams per cent. The smear showed 83 per cent polymorphonuclear cells, 2.5 per cent stab forms, 13 per cent lymphocytes, and 0.5 per cent monocytes. The non-protein nitrogen was 60 mg. per cent. The total serum protein was 5.80 grams per cent with 3.45 grams of albumin and 2.35 grams of globulin. The erythrocyte sedimentation rate was 42 mm. per hour corrected. The reticulocyte count was 4.4 per cent and the icterus index was 5. Serum agglutination for *P. tularensis* was negative. The urine was clear yellow with a specific gravity of 1.020, and pH of 5. It contained a moderate amount of albumin and a trace of sugar. Microscopic examination of the urine sediment was negative.

Course in the hospital. It was evident on admission that the patient was in a state of shock due to blood loss, and 500 c.c. of pooled plasma were given immediately after arrival on the hospital ward. Throughout the first hospital day the patient was given parenteral fluids and morphine sulfate. The impression at this time was that the patient had tularemia and as a complicating factor had bled profusely from an activated duodenal ulcer. The following day the patient's temperature had risen to 103.6° F., and the white cell count had dropped to 10,500 with an erythrocyte count of 1,100,000 and a hemoglobin of 5.5 gm. A transfusion of 500 c.c. of whole blood was given on the second hospital day.

The patient's abdomen had become much more distended and the tenderness less. Because of the marked abdominal distention and probable paralytic ileus, the question of perforation of the duodenal ulcer arose. Surgical consultation was obtained; it was felt at this time that the signs of peritoneal irritation were not of a degree to warrant the diagnosis of perforation. On the second day the non-protein nitrogen was 63. As there was no evidence of renal insufficiency, this was explained on the basis of blood in the gastrointestinal tract. Because of the continued abdominal distention, the following day a stomach tube was passed and connected to the Wangensteen suction apparatus. A rectal tube was inserted and prostigmine was given several times, with only slight relief of the distention. The Wangensteen suction brought back bile from the stomach, but no blood. The patient had had no bowel movement since admission and confirmatory evidence of bleeding into the gastrointestinal tract was still lacking. A small tap water enema was given without effect.

On the afternoon of the third hospital day the patient suddenly became dyspneic and three hours later there was dullness over the right chest extending in the midaxillary line from the level of the third interspace down to the base with fine moist râles throughout this area and in the right base posteriorly. Breath sounds were diminished. The respiratory rate was 40. It was felt at this time that the patient had developed tularemic pneumonia. A roentgenogram of the chest showed "an irregular pneumonia involving most of the right lung, somewhat deeply located. The left lung shows a moderately increased bronchovascular shadow with a little thicken-

ing around the left hilus. This is a pneumonia on the right and might well be tularemic pneumonia" (figure 1). Pneumococci, type XIII, were isolated in almost pure culture from the sputum. Because of this and as no laboratory evidence had been confirmatory of the diagnosis of tularemia, it was felt that treatment would have to be directed toward pneumococcic pneumonia, though the impression remained that the pneumonia was on the basis of tularemia. Consequently the patient was given penicillin, 15,000 Oxford units intramuscularly every three hours until the time of death. Following the development of pneumonia, a thoracentesis was done on the right side with the aspiration of 30 c.c. of dark, grossly bloody fluid which did not clot.

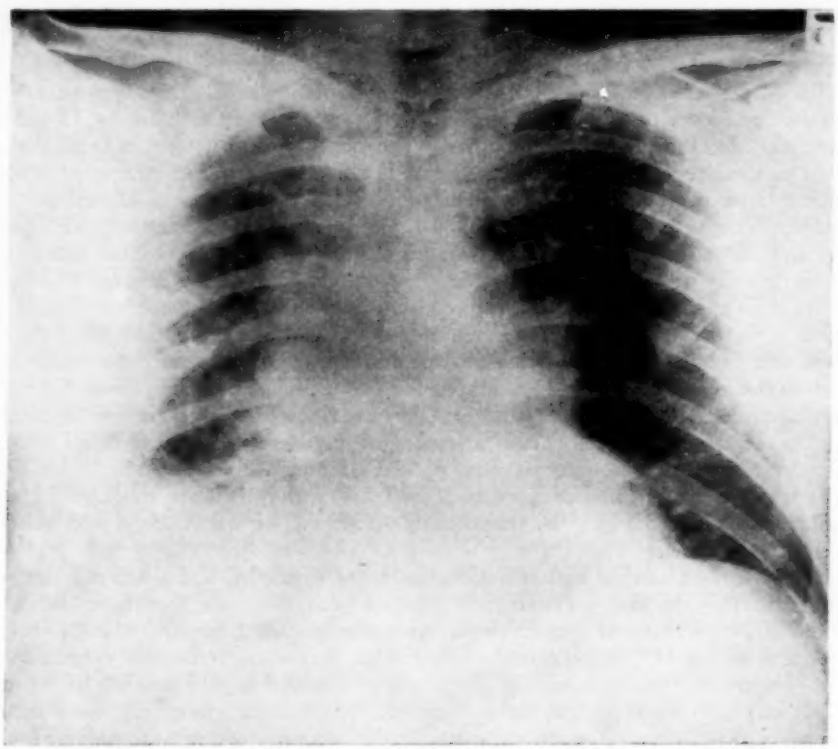

FIG. 1. Roentgenogram showing pulmonary infiltration due to tularemia.

On the third hospital day the patient received another transfusion of 500 c.c. of whole blood. The patient appeared definitely worse with the temperature remaining elevated to 104° F., and a white blood cell count of 10,500. Thoracentesis was again attempted on the right, but no fluid was obtained.

The following day, as the patient still had had no bowel movement and the distention persisted, an enema was given which was effective. The stool was yellowish brown, and the guaiac test for occult blood was negative. It was felt at this time that the patient had bled into the peritoneal cavity, but no signs of fluid intraperitoneally could be elicited. Exploratory laparotomy was considered, but was deemed unwise. Because of the marked abdominal distention, palpation of the abdomen was unsatisfactory. On the fourth hospital day the patient was given another transfusion of 500

c.c. of whole blood, following which the erythrocyte count was 3,440,000 and the hemoglobin 11.4 grams.

On the fifth hospital day the patient presented a typhoidal mental state with hallucinations and confused, incoherent talk. He appeared gravely ill, but was in no pain. On this day for the first time signs of free fluid in the peritoneal cavity were present though difficult to demonstrate because of the abdominal distention which had become worse. The pneumonia had extended upward in the right lung, and on the left there were numerous moist râles at the base posteriorly.

On the sixth hospital day the patient's condition rapidly became worse. He was markedly dyspneic, semi-comatose, and died a few hours thereafter. At the time of the patient's death there was still no laboratory evidence to support the diagnosis of tularemia. By the day following death the cultures of the pleural fluid obtained on the third hospital day had yielded growth of *P. tularensis*. Throughout the course of the illness no positive agglutination for *P. tularensis* was obtained.

Autopsy findings. The significant findings were as follows:

Peritoneal cavity: The peritoneal cavity contained about four liters of dark brownish-red fluid. This lay free and unclotted. In the upper abdomen was gelatinous, dark-red clotted blood which was loosely attached to the stomach, omentum and transverse colon. Although the serosal surfaces were edematous and slightly icteric, there was no evidence of purulent exudate. Further exploration of the upper abdomen revealed a large, swollen, pale liver. Beneath its capsule were a few extremely minute yellowish-gray opacities. These were less than 1 mm. in diameter and barely visible. It was apparent that the liver had been displaced to the right by a large bloody mass which lay in the left upper quadrant. Much of this was fresh, dark red, easily removed elastic clot. When this was stripped away, the rounded edge of the spleen became visible. The thin tense capsule was torn in several places. The splenic vein was exposed and traced to the splenic hilum. During this procedure the spleen was rotated in order to expose the hilum. In attempting to remove the spleen the organ was found to be torn almost in half. The spleen and the associated hematoma weighed 1,000 grams. The anterior half consisted of tense, thin capsule, torn in several areas, which covered gelatinous, dark red blood clot. No splenic tissue was seen in this portion. The posterior portion consisted of spleen, freshly clotted blood, and a laminated, friable, gray and red blood clot. Most of the hemorrhage had occurred between the pulp and the capsule so that there was an enormous subcapsular hematoma which had torn the capsule. The pulp istelf was rather soft and pink. Within it one could see the chalky opacities so characteristic of tularemia (figure 2).

Pleural cavities: Each pleural cavity contained about 100 c.c. of blood-tinged unclotted fluid, which contained no fibrin. A few ecchymoses were seen near the pleuro-pericardial reflection.

Lungs: There was moderate atelectasis in each lung. Before they were removed a raised area 2 cm. in diameter in the right middle lobe was seen. Its edges were sharply circumscribed, and on the dull overlying pleura were a few strands of fibrin. This lesion was very firm and unyielding in consistency, and was near the tip of the middle lobe. Two similar lesions were seen in the right lower lobe. Another was felt in the left lower lobe near the medial border. Sections of these lesions had the general shape of infarcts. Their surfaces were raised and dry. Scattered throughout them were yellow opacities about 1 or 2 mm. in diameter. There was some clustering of these to form much larger opaque masses (figure 3). Aside from these specific lesions the lungs showed only atelectasis. There were no areas of ordinary pneumonia. The bronchi contained small quantities of mucus. The larger pulmonary arteries and veins were not remarkable. There was considerable enlargement of the tracheobronchial nodes on each side. They were swollen and moist, and on cut

section a few questionable opacities which suggested necrosis were seen, but the major portion of the cut surface appeared quite moist, and almost gelatinous.

Gastrointestinal tract: No ulcer or scar was seen either in the stomach or duodenum.

Liver: The organ weighed 2150 grams. It was swollen and pale. Through the thin opalescent capsule the minute opacities already described were visible. Cut sections revealed a pale, lusterless, yellowish-tan parenchyma with prominent central veins. Here also a few opaque yellow areas of necrosis were seen.

Microscopic notes. The spleen and liver showed the characteristic areas of focal necrosis seen in tularemia. The lesions in the liver were in the process of resolution. Most of the necrotic debris had been removed in some of the lesions, and there was

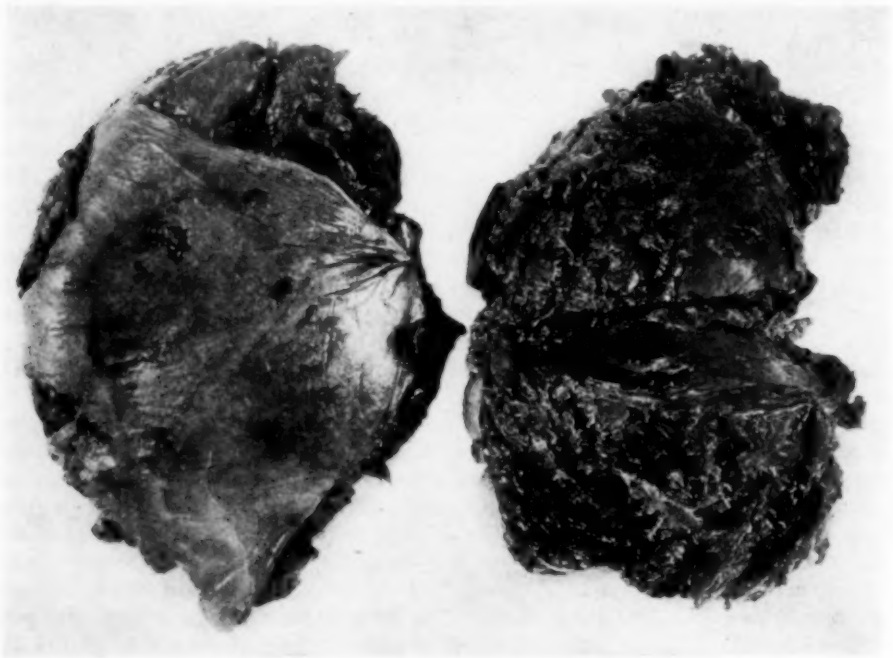

FIG. 2. Photograph of ruptured spleen showing anterior and posterior portions. See text.

definite evidence of fibrosis. There was no artery in the sections of spleen which might have served as the site of initial hemorrhage.

The pulmonary lesions were also characteristic of tularemia, but they were of such a complex nature that they will be described in a separate paper.

Bacteriological findings. Four mice were inoculated intraperitoneally with 0.1 c.c. of emulsified splenic tissue. All of the mice became sick and died on the fourth day. Autopsy revealed markedly enlarged spleens which were studded with large, opaque, yellowish areas. Smears from this tissue stained by Wright's method showed innumerable intracellular short bacillary forms crowding the cytoplasm of large mononuclears. The bacilli were gram-negative. On cystine-dextrose-blood agar slants inoculated with particles of mouse spleen soft gray colonies of small gram-negative bacilli appeared in 48 hours. No growth was obtained on cystine-free blood agar. The microörganisms were agglutinated to titer in known anti-tularense agglutinating serum.

Pleural fluid, aspirated three days before death of the patient, cultured on cystine-dextrose-blood agar was positive for *P. tularensis* on the following fourth day or one day after the patient's death. These microörganisms also agglutinated to titer in known anti-tularense agglutinating serum.

FIG. 3. Photograph of cut section of right lung showing characteristic gross lesions of tularemia.

COMMENT

The diagnostic problem in this patient was rendered difficult by the fact that a hemorrhagic crisis occurred during the course of the illness. Although no direct evidence for gastrointestinal hemorrhage could be elicited, neither could

completely valid reasons be obtained for supporting a diagnosis of massive intraperitoneal hemorrhage. The reliable evidence of a previous and possible persistence of a peptic ulcer added to the difficulty. Nevertheless, the history of handling wild rabbits and the development of the ulcero-glandular disease with subsequent pulmonary involvement presented almost adequate evidence for tularemia in spite of the absence of laboratory confirmation in the form of agglutinating antibodies against *P. tularensis*. Although in most instances these antibodies can be demonstrated in the third week of the disease, cases in which agglutinins cannot be demonstrated at this time are encountered.[1, 2] Positive culture from the pleural exudate grew out too late in this case to support the clinical diagnosis of tularemia.

The pathogenesis of massive intrasplenic hemorrhage with subsequent splenic rupture in this instance although unusual, can nevertheless be postulated if the behavior of *P. tularensis* in the disseminated disease is considered.[3] The focal areas of necrosis in various tissues and organs apparently have their origin as miliary intracapillary or perivascular areas of inflammatory reaction initiated by the presence of the microörganisms in these environments favorable to their proliferation.[4] Rapid focal destruction of tissue can and does involve vascular walls as evidenced by hemorrhage and thrombosis in areas involved by the infection.[4] That larger vessels such as intrasplenic veins may become involved in a focal destructive process of this type is not surprising; in fact, it is perhaps more surprising that such circumstances do not occur more frequently. Once a larger vessel wall has been broken down by this process, the subsequent hemorrhage into and resulting rupture of the spleen can be readily envisaged.

The gross pathological features in the lungs and liver in this case were characteristic of those found in tularemia.[5, 6] The peripherally located, sharply circumscribed, firm, infarct-like areas of pulmonary inflammatory reaction may be considered as almost pathognomonic, as are the yellow or chalk-like areas of necrosis in the liver and spleen nearly always associated with this disease.

Since there seems to be every reason to believe that an occurrence of this type may develop in other cases of tularemia this detailed report has been made. The symptoms attendant upon this complication may present many confusing problems unless the possibility of its occurrence is considered.

Summary

1. The clinical and postmortem features of a case of splenic rupture due to tularemia are described. A survey of the literature reveals no similar previously reported case.

2. The pathologic features of the pulmonary lesions in this case at autopsy were so characteristic of tularemia that a gross diagnosis of the disease could be established before laboratory confirmation by isolation and identification of the microörganism was possible.

BIBLIOGRAPHY

1. Ransmeier, J. C., and Ewing, C. L.: The agglutination reaction in tularemia, Jr. Infect. Dis., 1941, lxix, 193–205.
2. Kennedy, J. A.: Pulmonary tularemia, Jr. Am. Med. Assoc., 1942, cxviii, 781–787.

3. Foshay, L.: Tularemia: A summary of certain aspects of the disease including methods for early diagnosis and the results of serum treatment in 600 patients, Medicine, 1940, xix, 1–83.
4. Goodpasture, E. W., and House, S. J.: The pathologic anatomy of tularemia in man, Am. Jr. Path., 1928, iv, 213–226.
5. Francis, Edward, et al.: The pathology of tularemia, Natl. Inst. Health, Bull. No. 167, 1937, Washington.
6. Intrathoracic changes in tularemia, Med. Bull. Vet. Admin., 1934, xi, 77–83.

DISSEMINATE LUPUS ERYTHEMATOSUS UNSUCCESSFULLY TREATED WITH PENICILLIN, ROENTGEN-RAY CASTRATION AND SERUM ALBUMIN *

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Disseminate lupus erythematosus is a systemic disease which may be acute, subacute or chronic. Manifestations are commonly found in the skin, joints and viscera. Sixty to 80 per cent of the cases of the disseminate form occur in females during the second and third decades of life.[1] The mortality rate in the subacute form is about 50 per cent, whereas in the acute form it is reported as invariably fatal.[2] The etiology and pathogenesis of this disorder are still unknown. Stokes and associates [3] have attempted to integrate the variegated manifestation of lupus erythematosus on an infection-allergy basis with major involvement of the vascular system and the skin. Klemperer and associates [4] have suggested that the primary pathologic lesion of the disorder is located in the connective tissue systems of the body, expressing itself as a fibrinoid degeneration of the collagenous fibers probably due to physio-chemical changes in the colloidal state of the connective tissue. No specific therapy has been found.

The following case report is that of typical subacute disseminate lupus erythematosus unsuccessfully treated with penicillin and roentgen castration.

Case Report

The patient was a 32 year old Negro female, who was in good health until June 1944, at which time she complained of vague, intermittent low back pain. There was no history of unusual exposure to sunlight nor of photosensitivity. In July 1944 she observed the appearance of symmetrical erythematous lesions on both elbows, and later a similar erythematous patch that was of a butterfly pattern which bridged the nose and tended to spread toward the malar eminences. Concomitantly, a similar rash appeared on the scalp which eventually became scaly with associated falling of the hair. In September 1944 she noted occasional facial edema and slight puffiness of the eyelids upon arising each morning and a few weeks later, slight intermittent pedal edema, more pronounced at night. About this time there appeared a generalized lymphadenopathy; the largest nodes, about 1.5 cm. in diameter, were present in the cervical areas. They were firm, freely movable and non-tender. Other physical findings were not significant at the time of this examination in October. Hematological studies showed a normal hemogram and normal blood chemistry (see table). The corrected sedi-

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From the Department of Medicine, Howard University, School of Medicine, and Freedmen's Hospital, Washington, D. C.

mentation rate was 3 mm. in one hour. Urinalysis and blood Wassermann reaction were negative.

TABLE I

Hemogram and Blood Chemistry during Course of Disease

Date	R. B. C. (Millions)	W. B. C.	Sed. Rate per Hr. Corrected	Tot. Protein gm. %	A/G ratio	N.P.N.	Creatinine
11–16–44	4.22	6,400	3 mm.	6.1	1.65	29	
1–6–45	3.50		10 mm.	5.0			
2–18–45				4.43	0.98	43	1.8
2–21–45	3.90	7,600					
3–7–45	2.60	11,300		5.38	0.46	95	3.0
3–10–45						127	2.7
3–12–45				4.59	0.93	219	6.0
3–15–45				4.93	0.88	92	3.0
3–19–45				4.72	1.42	98	
3–22–45				5.01		96	1.6
3–29–45	2.80	13,800		4.19	1.40	115	4
4–1–45	2.56	18,050	21 mm.*				
4–2–45				4.84	0.99	121	5

* Uncorrected.

In November 1944 the patient developed slight tenderness in the right upper quadrant and an enlarged liver, three fingers'-breadth below the right costal margin. At this time her temperature ranged from 99° to 101° F. The only new complaints were intermittent arthritic pains in the shoulder, wrists, elbows and fingers, migratory in nature. A biopsy of one of the largest lymph nodes showed only lymphoid hyperplasia, not conforming to any definite pathologic pattern. Also, a biopsy of one of the skin lesions showed no diagnostic changes. The patient was given 500,000 units of penicillin intramuscularly, 20,000 units every four hours with no change in her condition. In addition, she was given blood transfusions, thiamine hydrochloride, and crude liver extract.

In December, she developed a left pleural effusion. The liver extended about four fingers'-breadth below the costal margin and there was a slight amount of abdominal fluid. She developed a persistent anorexia and nausea.

During January and February 1945 the patient was studied by Dr. Edward Rose at the University of Pennsylvania Hospital, who confirmed the diagnosis of disseminate lupus erythematosus.

In addition to supportive therapy, the treatment there consisted of a course of iodides and roentgen-ray castration. The castration therapy was instituted because of previous observations by Rose and Pillsbury [5] suggesting a possible relationship between ovarian function and lupus erythematosus. The skin lesions showed some improvement under the iodide therapy, but there was progression in the systemic manifestations including anemia, hypoproteinemia and evidence of renal involvement. At this time she showed casts in the urine, proteinuria and microscopic hematuria.

The patient was readmitted to Freedmen's Hospital, February 18, 1945 at which time she showed generalized edema, anemia (see table) and dyspnea. There were signs of bilateral pleural effusion and ascites. The scalp lesions had resulted in several areas of alopecia. Because of the severe hypoproteinemia—4.43 grams per 100 c.c.; A/G ratio of 0.98—she was given serum albumin. A total of 400 grams was given during a period of 16 days beginning March 10, 1945. A slight rise both in the total protein and the A.G. ratio occurred but without change in the edema or effusions. An attempt to produce diuresis by mercupurin and ammonium chloride was

made. Two ampules of mercupurin in 20 c.c. of distilled water were given intravenously on Feb. 25, March 2, and March 5, 1945, while the patient was taking 4 gm. of ammonium chloride daily. No diuresis occurred. The significant change which did occur was an increase in nitrogen retention (see table).

The course in the hospital was gradually downward. Her temperature ranged from 100° to 101° F. A blood culture on March 7, 1945 was negative. About March 15, 1945 the patient developed a sore throat which became more severe. This was treated unsuccessfully with sulfadiazine. On March 27, 1945 a blood culture positive for *Staphylococcus aureus* was obtained. At this time she developed a transitory pleuropericardial friction rub. The patient died in uremia April 3, 1945, approximately 10 months after onset of initial symptoms. Postmortem examination could not be obtained.

Summary

A typical fatal case of subacute disseminate lupus erythematosus is presented. The total duration of illness was about 10 months. The initial lesion developed on the skin, and later clinical signs of involvement of the joints, pleura, liver and kidneys were present. A gradually progressive hypoproteinemia developed with associated generalized edema, ascites, and pleural effusion. No clinical improvement resulted from the administration of 400 grams of serum albumin during a

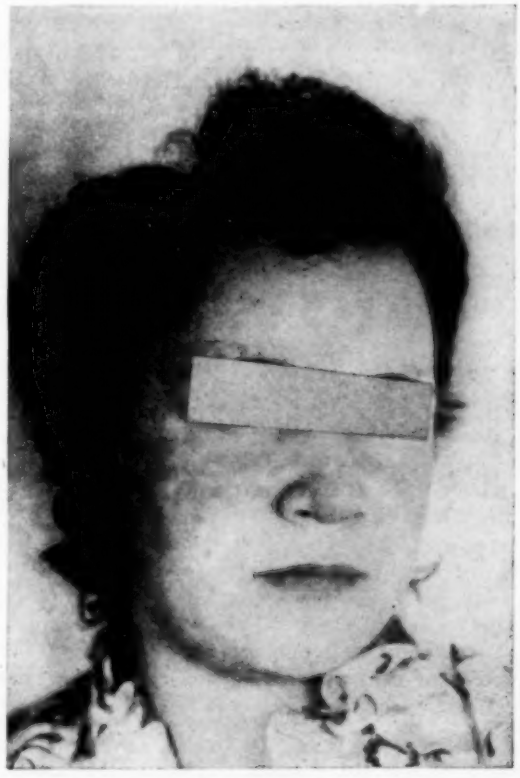

Fig. 1. Photograph showing symmetrical erythematous lesions of the nose and cheeks.

period of 16 days. The anemia was progressive, leukocytosis was present only during the last month of illness, a low grade fever was constant but the sedimentation rate was not elevated. Penicillin and roentgen castration gave no beneficial effect. Several days after mercupurin intravenously the non-protein nitrogen became elevated. There was some subsequent drop in the non-protein nitrogen but not to normal. The patient died in uremia.

BIBLIOGRAPHY

1. MONTGOMERY, HAMILTON: Pathology of lupus erythematosus, Proc. Staff. Meet. Mayo Clin., 1940, xv, 679.
2. KIERLAND, R. R.: Classification and cutaneous manifestations of lupus erythematosus, Proc. Staff. Meet. Mayo Clin., 1940, xv, 675.
3. STOKES, JOHN H., BEERMAN, HERMAN, and INGRAHAM, NORMAN R.: The "lupus erythematosus" concept: an attempt at integration, Am. Jr. Med. Sci., 1944, ccvii, 540.
4. KLEMPERER, P., POLLACK, A. D., and BAEHR, G.: Diffuse collagen disease; acute disseminated lupus erythematosus and diffuse scleroderma, Jr. Am. Med. Assoc., 1942, cxix, 331.
5. ROSE, EDWARD, and PILLSBURY, DONALD M.: Lupus erythematosus (erythematodes) and ovarian function: observations on a possible relationship, with report of six cases Ann. Int. Med., 1944, xi, 1022.

BILATERAL SUBDURAL HEMATOMA—AN UNUSUAL COMPLICATION OF MENINGOCOCCUS MENINGITIS *

By JACK NELSON, M.D., ROBERT M. CLYNE, M.D., and J. GEORGE SHARNOFF, M.D., *New York, N. Y.*

CASE REPORT

History: C. O., a 41 year old male, was admitted to Lincoln Hospital on November 14, 1944 with a five day history of chills and fever together with "red-colored" urine. Two days subsequently he began to have generalized aches and pains. On the day of admission he became increasingly weak, fell to his knees, and was brought to the hospital.

Physical Examination: The patient appeared acutely ill but alert and oriented. The temperature was 104.4° F.; the pulse was 120. The respirations were 40 per minute, and the blood pressure was 102 mm. Hg systolic and 70 mm. diastolic. There was slight infection of the throat. The heart and lungs were clear, and the abdomen was normal. The deep tendon reflexes were equal and active throughout. There were no abnormal reflexes. The neck was flaccid, and there were no other signs of meningeal irritation.

Laboratory Examination: The urine contained 15 erythrocytes per high power field but was otherwise normal. The blood showed: hemoglobin 90 per cent (Sahli), leukocytes 16,800, polymorphonuclears 86 per cent (including 14 per cent immature forms), lymphocytes 12 per cent, monocytes 2 per cent. A roentgenogram of the chest was normal with respect both to heart and lungs. The blood urea nitrogen was

* Received for publication September 10, 1945.
From the Medical Service of Dr. Kenneth Taylor, Lincoln Hospital, New York City, N. Y.
Dr. Robert O. Kellog, Jr. participated in the clinical management of this case.

25 mg. and the blood sugar 102 mg. per 100 c.c. The blood Kline reaction was negative.

Course: On symptomatic therapy including aspirin there was temporary improvement. However, on the second hospital day the temperature rose to 102.4° F., the patient became stuporous, and the neck was suggestively rigid. A lumbar puncture revealed cloudy fluid with an initial pressure of 280 mm. of water. There were 20,000 leukocytes per cu. mm. with a large predominance of polymorphonuclear cells. The protein was 942 mg. per 100 c.c. and the sugar was less than 10 mg. per 100 c.c. Both smear and culture of the cerebrospinal fluid and culture of the blood revealed meningococcus Group I.

Sulfadiazine therapy was instituted at this time; 5 gm. were given intravenously as an initial dose, and this was followed by 1 gm. intravenously every four hours. On the third day of hospitalization the patient appeared worse, with a temperature of 103.4° F. and marked meningeal signs. The eyes were deviated to the left, and there was a fine horizontal nystagmus. There were also a right central facial paresis and a paresis of the right arm and leg. The right abdominal reflex was absent, and there was a right Babinski reflex. Lumbar puncture at this time revealed fluid which was still grossly purulent and was positive for meningococci on smear and culture.

In addition to the sulfadiazine therapy which was continued at the rate of 1 gm. every four hours, penicillin was administered at the rate of 20,000 units intrathecally once daily and 20,000 units intramuscularly every three hours. During the following two days, despite the persistence of neurologic signs and the maintenance of the temperature in the range between 101.0° and 103.5° F., the patient seemed improved with respect both to his mental state and his general condition. However, on the evening of the fifth hospital day the patient began to have generalized convulsive seizures with greater involvement of the right side. These recurred approximately every 10 to 20 minutes. Fluid obtained by lumbar puncture during this period was still cloudy but less so than previously. The initial pressure was 130 mm. of water. There were 6,650 polymorphonuclear cells per cu. mm. The protein was 540 mg. and the sugar was still less than 10 mg. per 100 cu. mm. A few meningococci were seen on smear but the culture was sterile. Despite continued therapy with sulfadiazine and penicillin the convulsions persisted for the next 30 hours until the patient died on the seventh hospital day.

Pathologic Report: Postmortem examination was performed eight hours after death. On external examination the body was that of a well developed, well nourished male. The skin was clear. The right pupil was slightly more dilated than the left.

Gross Pathology: Heart: The heart was normal in size and configuration and revealed a small triangular area of myocardial fibrosis in the lateral wall of the left ventricle. *Lungs:* Several small patches of pneumonic consolidation were noted in the mid-portion of the upper lobe of the right lung. The tracheobronchial membranes were markedly reddened. *Liver, Spleen, Pancreas* and *Adrenals:* These organs revealed nothing remarkable.

Kidneys: The kidneys were of normal size and configuration. Several small mucosal hemorrhages were noted in the calyces and pelves of both kidneys.

Gastrointestinal Tract: Two cm. above the pylorus on the posterior wall was a shallow, somewhat irregular ulceration of the gastric mucosa measuring 0.5 cm. in diameter. The base of the ulcer revealed a deep brown pigmentation. Immediately beyond the pyloric ring there was seen a second, deeper ulcer measuring 1.3 cm. in diameter. The edge of this ulcer was smooth and thickened. The lower half of the jejunum and the entire ileum were filled with tarry material.

Brain: When the dura mater was opened, two large, flat masses of recently clotted blood, one over each hemisphere, were found in the subdural space over the convex cerebral surfaces. The blood clot on the left was somewhat larger. The

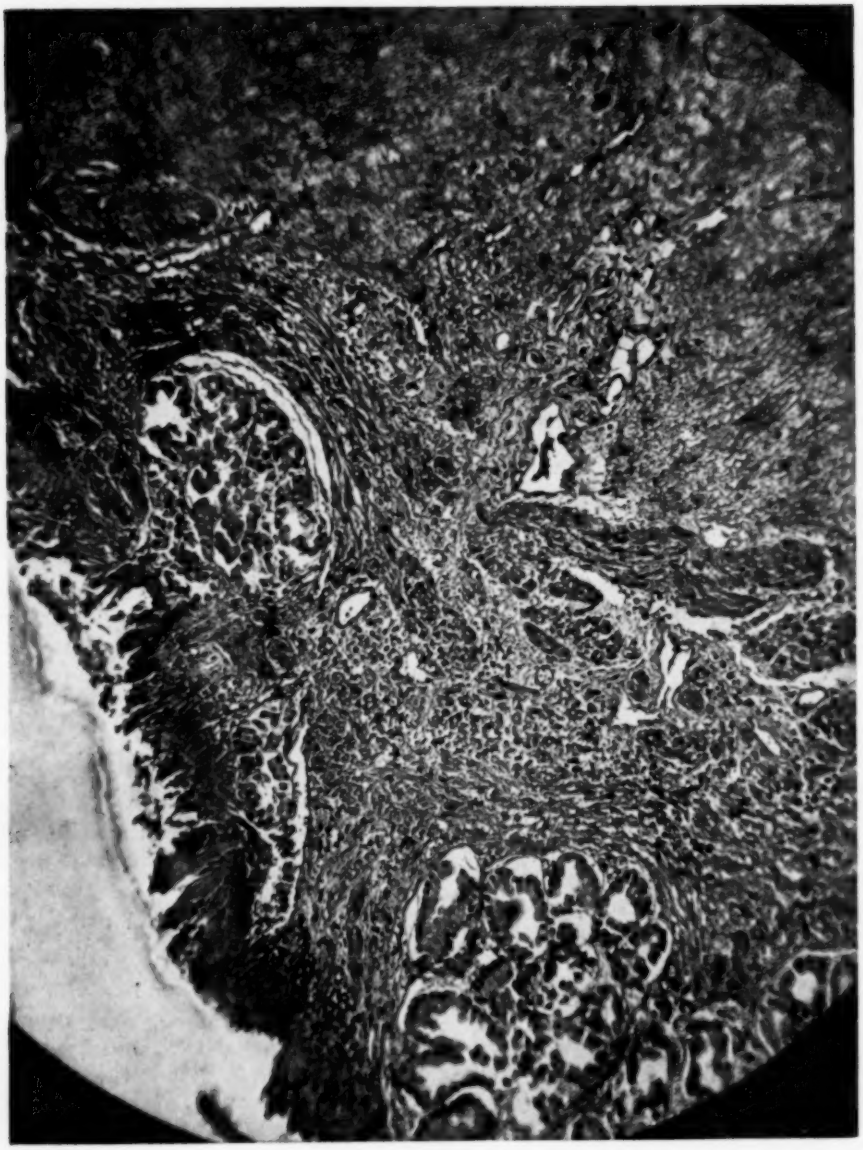

FIG. 1.

leptomeninges were greatly thickened by a greenish-yellow, gelatinous material. Cut sections of the brain were normal.

Histopathology: Lungs: There was an exudate of polymorphonuclear cells and fibrin in the bronchioles and in a moderate number of alveoli in sections taken from the right upper lobe.

Stomach: The mucosa and muscularis mucosa were eroded in the areas of ulceration. The submucosa was markedly edematous. The blood capillaries in the base of the ulcers were greatly distended by coagulated blood. A small amount of fibrosis was seen (figure 1).

Brain: The blood vessels of the leptomeninges were markedly dilated, the tissues edematous. A moderate number of degenerating polymorphonuclear cells and lymphocytes were seen. The cytoplasm of these cells was vacuolated, and many of the nuclei were undergoing karyolysis (figure 2).

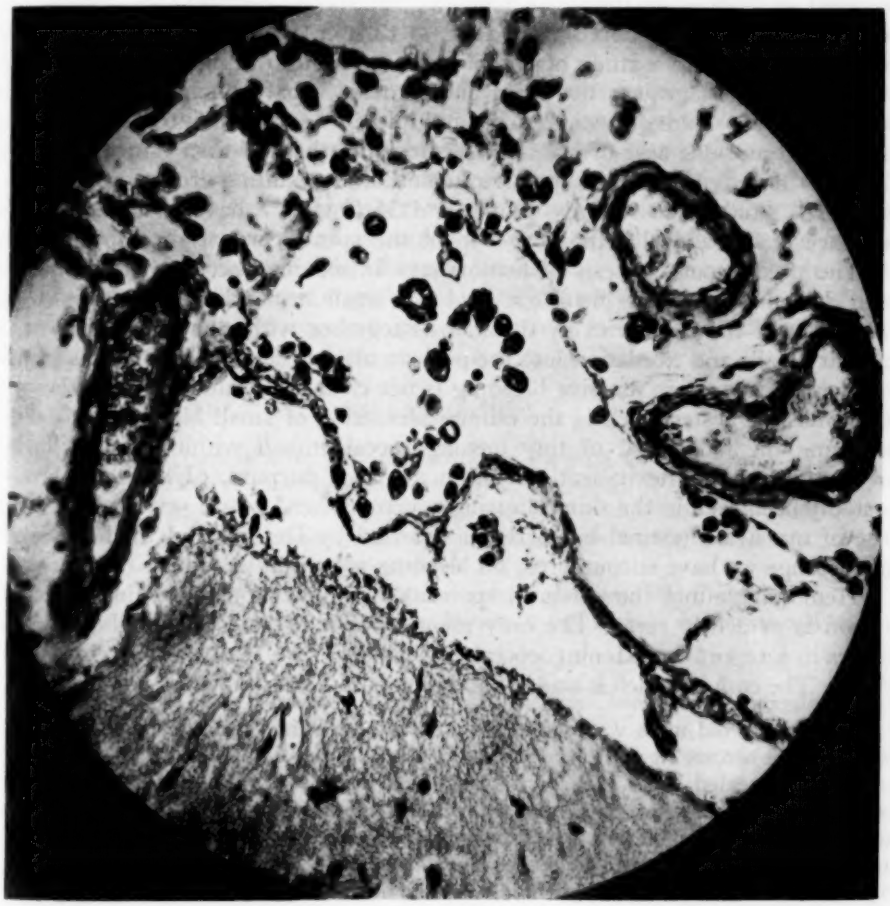

FIG. 2.

DISCUSSION

It was evident from the autopsy examination that the meningococcus meningitis had almost entirely subsided. No organisms were seen on histologic sec-

tion, and the exudate was that of a process undergoing resolution. The outstanding feature of the case at the time of death was the finding of multiple hemorrhages. There was bleeding into the subdural space and intestinal lumen and, to a lesser degree, into the mucosa of the genito-urinary tract. Death resulted from the massive subdural hemorrhages, and for this bleeding no obvious source could be determined.

That a hemorrhagic tendency is part of the syndrome of meningococcal infections has been evident since the earliest reports of this disease drew attention to the purpuric nature of the rash. However, the frequency and variety of these hemorrhages have often gone unrecognized. The first case of hemorrhage into the adrenal glands consequent upon meningococcal infection (the condition subsequently to be associated with the names of Waterhouse and Friderichsen) was reported in 1894.[1] In the years following, epistaxis, hematemesis, melena and hematuria were encountered from time to time in patients having this disase. In 1916 Denehy,[2] in a study of an epidemic occurring during World War I, alluded to hemorrhage into the brain and into the subarachnoid space. He also described two striking instances of multiple hemorrhages into the substance of the lung and one case of massive bleeding into the intestinal lumen. In 1922 Gordon[3] reported a case of massive hemothorax resulting from meningococcal infection. And more recently Banks and McCartney[4] have described the occurrence of extradural hemorrhage about the spinal cord at the thoracic level.

The precise pathogenesis of hemorrhage in meningococcal infection has not been determined.[5] The histologic study of small hemorrhages[6] reveals an involvement of the capillaries by thrombosis together with cloudy swelling of the capillary walls and exudation into the perivascular spaces. Whether this process is adequate to explain massive bleeding is not clear. An alternative explanation which has suggested itself is the minute ulceration of small blood vessels either following the lodgement of tiny meningococcal emboli within the capillaries[7] or on the basis of devitalization within areas of purpura. Ulceration has repeatedly been seen in the skin following severe rashes.[8] And yet often, as in the case of massive intestinal hemorrhage reported by Denehy and in the subdural hemorrhage we have encountered, no bleeding point can be found.

Hemorrhage into the subdural space as a complication of meningococcal infection is evidently rare. The only mention of it to be found in the literature occurs in a report on "Meningococcal Encephalitis" by Banks and McCartney in 1942. The case in which it was noted deserves to be described in some detail.

A 19 year old male was admitted to the hospital in coma. Thirty hours previously he had become ill and 11 hours before admission he had lapsed into stupor. Examination revealed coma with restlessness and rigidity of the neck. There was no papilledema. The right pupil did not react to light. The cerebrospinal fluid was under a pressure of 300 mm. of water. Meningococci were found on smear and culture. A course of sulfathiazole therapy was begun. On the second hospital day a right lower facial paresis appeared. On the third hospital day coma persisted, and the respiration remained stertorous. The cerebrospinal fluid was salmon-pink in color and had 12,000 cells. Meningococci were observed on smear, but culture proved sterile. During this day there was moderate improvement; the patient became oriented and "spoke a few words." On the fourth and fifth hospital days, however, there was a relapse into deep coma, breathing became stertorous again, and the pupils appeared dilated and fixed. The cerebrospinal fluid was again salmon-pink in color

and under high pressure. The cells had decreased to 5,300 and, although meningococci were found on smear, culture again proved sterile. During the following day there appeared convulsions, hyperthermia (temperature 107° F.) and death.

Autopsy revealed a subdural hematoma two inches long over the left temporal lobe. There was a very scanty purulent exudate over the base of the brain and within the ventricles. The brain and spinal cord were congested and edematous, and a small hemorrhage was found in the mid-brain.

It will be observed that the case we are reporting and the one just summarized bear a marked similarity with respect to certain clinical features. The syndrome of meningitis was predominant during the early course of both cases. Furthermore, in both instances there was transient clearing of the mental state together with suggestive evidence that the meningitis was beginning to come under control (falling leukocyte count and sterile culture). And following this, both patients returned to coma with an increase of general and focal neurologic signs leading to death.

It should be pointed out that this pattern of events is in contrast to the expected course of meningococcus meningitis. It has been our experience that the meningitis of itself almost invariably responds promptly to adequate sulfonamide therapy and that, having responded, it does not relapse.[9] On the other hand, hemorrhagic encephalitis, when it occurs as a complication of meningococcal infection, comes at the onset and is rapidly fatal. It is obvious that the clinical differentiation of subdural hematoma from the context of meningitis or from the complication of hemorrhagic encephalitis presents considerable difficulty. Yet the timely employment of neurosurgery is so effective in the treatment of such hematoma that the diagnosis of this condition may be life saving.

BIBLIOGRAPHY

1. Voelker, A. F.: Item in Path. Reports Middlesex Hospital, 1894, p. 246.
2. Denehy, W. J.: Epidemic cerebrospinal meningitis, Brit. Med. Jr., 1916, ii, 684.
3. Gordon: 1922 (Quoted from Briton—reference below).
4. Banks, H. S., and McCartney, J. E.: Meningococcal encephalitis, Lancet, 1942, i, 219.
5. Briton, D.: Cerebrospinal fever, 1941, London, 152 pp.
6. (a) Netter, A., and Debré, R.: La méningite cérébrospinale, 1911, Paris.
   (b) Banks, H. S., and McCartney, J. E.: Meningococcal adrenal syndromes and lesions, Lancet, 1943, i, 711.
   (c) Reference 4, above.
7. Murray, E. G. D.: The Meningococcus Medical Research Council Special Report Series, No. 124, H. M. Stationery Office, London, 1929.
8. Worster-Drought, C., and Kennedy, A. M.: Cerebrospinal fever, 1919, A. and C. Black, London.
9. Appelbaum, E., and Nelson, J.: Sulfadiazine and its sodium compound in the treatment of meningococcic meningitis and meningococcemia, Am. Jr. Med. Sci., 1944, ccvii, 492.

EDITORIAL

THE CONCEPT OF HYPERSPLENISM

THE intimate relationship of the spleen to hematopoiesis has been recognized for many years. This correlation has been exemplified in the past by the catch-all term *splenic anemia* formerly widely used to describe almost any syndrome characterized by splenomegaly and anemia. However, in contradistinction to the many recent advances in knowledge of the normal and pathological physiology of other organs and systems, information concerning the activities of the spleen has been relatively scanty. Such information as has accumulated has often been deduced from observations made in pathological states. The concept of hypersplenism is typical of this approach.

In 1916 Kaznelson [1] demonstrated that the removal of the spleen resulted in a prompt rise in the peripheral platelet count and consequent clinical improvement of some cases of thrombocytopenic purpura. It was postulated that the spleen exerted an excessive cytolytic effect upon platelets. However, following the widespread use of bone marrow study in such cases in recent years megakaryocytic hyperplasia has been regularly observed in essential thrombocytopenic purpura. Two schools of thought exist as to the pathogenetic mechanism: (1) that the hyperplasia is a compensatory phenomenon resulting from excessive phagocytosis of circulating platelets, or (2) that it represents maturation arrest due to excessive inhibition by an overactive spleen. Recent studies by Dameshek and Miller [2] demonstrate not only quantitative alterations in megakaryocytes but well-defined qualitative changes characterized chiefly by lack of platelet formation from the cytoplasm of these cells. Since removal of the spleen results in prompt and dramatic change in the megakaryocytes with the outpouring of platelets into the peripheral blood it is suggested that recovery is essentially due to the removal of an overactive splenic humoral, possibly hormonal, substance, i.e., splenectomy results in the correction of a state called with some propriety, hypersplenism.

That an intimate relationship exists between the spleen and the level of granulocytes in the peripheral blood is evidenced by the effect of removal of the normal spleen in the experimental animal and in man. Extirpation of the spleen results in a prompt and often quite marked granulocytic leukocytosis which may persist for some time. Frank [3] in 1916 first described an entity which he named *aleukia splenica* and which apparently escaped

[1] KAZNELSON, P.: Verschwinden der hämorrhagischen Diathese bei einem Falle von "essentialler Thrombopenie" (Frank) nach Milzexstirpation. Splenogene thrombolytische Purpura, Wien. klin. Wchnschr., 1916, xxvi, 1451–1454.

[2] DAMESHEK, W., and MILLER, E. B.: The megakaryocytes in idiopathic thrombocytopenic purpura, a form of hypersplenism, Blood, 1946, i, 27–51.

[3] FRANK, E.: Aleukia splenica, Berl. klin. Wchnschr., 1916, liii, 555.

widespread clinical recognition until recently when Doan and Wiseman [4] clearly delineated the clinical and hematological features of a syndrome called by them *primary splenic neutropenia.* The syndrome is characterized by marked leukopenia, splenomegaly and a normal or even hyperplastic marrow. The existence of neutropenia predisposes to recurring episodes of pyogenic infection. Acute, subacute and chronic varieties have been described. Splenectomy, performed after careful studies have ruled out other pathological states, results in prompt rise in the leukocyte count and clinical improvement of the patient. The effect is fully as dramatic as that observed in essential thrombocytopenic purpura. To date approximately twelve such cases have been recorded in the literature by a number of observers.

No information exists yet as to the initiating causes. Doan and Wiseman describe excessive phagocytosis of leukocytes by reticulo-endothelial cells of the pulp studied by a supravital staining technic. Routine histopathological studies of the spleen usually fail to demonstrate significant changes. A humoral or hormonal mechanism is again postulated and the syndrome is regarded as an example of hypersplenism in which the inhibitory effect is directed almost entirely against the neutrophilic leukocytes.

In some of the recorded cases of splenic neutropenia associated moderate reduction in the erythrocyte and platelet counts has been observed. A logical extension of the concept of hypersplenism would be a syndrome characterized by depression of all cellular elements derived from the bone marrow. Such an entity has recently been described by Doan and Wright [5] and is referred to as *primary splenic panhematopenia.* Two cases are reported, one an apparently congenital variety, the other an acute form. The clinical importance of the recognition of this entity lies in its separation from the general group of inevitably fatal aplastic anemias. Although *primary splenic panhematopenia* probably constitutes but a small fraction of such cases, the vastly improved prognosis after splenectomy renders their separation imperative.

It is obvious from consideration of the accumulated data, that the spleen has more than a passive function as a reservoir of red blood cells or even as the "graveyard" of erythrocytes. Evidence indicating a possible endocrine function is still scanty. Such a possibility has been postulated for a number of years but no valid proof existed. Within recent years a few bits of data have accumulated. Thus in 1938 Troland and Lee [6] reported the isolation of a substance from acetone extracts of spleens removed for essential thrombocytopenic purpura which induced temporary reduction of the platelet count after injection into animals. The existence of "Thrombocytopen,"

[4] WISEMAN, B. K., and DOAN, C. A.: Primary splenic neutropenia; a newly recognized syndrome, closely related to congenital hemolytic icterus and essential thrombocytopenic purpura, Ann. Int. Med., 1942, xvi, 1097–1117.

[5] DOAN, C. A., and WRIGHT, C. S.: Primary congenital and secondary acquired splenic panhematopenia, Blood, 1946, i, 10–26.

[6] TROLAND, C. E., and LEE, F. C.: Thrombocytopen. A substance in the extract from the spleen of patients with idiopathic thrombocytopenic purpura that reduces the number of blood platelets, Jr. Am. Med. Assoc., 1938, cxi, 221–226.

as it was named, has been a moot question. Its status is still disputed at this time. Dameshek [2] has reported recently that saline extracts of similar spleens produced profound thrombocytopenia with characteristic bone marrow changes in dogs. Evidence of another sort has recently been contributed by Ungar.[7] He reports the isolation of a crystalline substance from guinea pig spleen which he terms "Splenin." This substance reduces the bleeding time, and increases capillary resistance in the experimental animal. Its secretion into the blood is believed to be part of the pituitary-adrenal response to stress. Splenectomized animals injected with cortico-trophic hormone or adrenal cortical extract do not display the characteristic drop in bleeding time observed in normal animals. Ungar believes that these studies demonstrate clearly an endocrine function of the spleen. What relation, if any, exists between "Thrombocytopen" and "Splenin" is not clear at this time.

If the concept of hypersplenism is further supported by experimental data one might be justified in postulating a eusplenic and even a hyposplenic state. At this time it would be obviously impossible to do more than speculate upon the probable clinico-pathological manifestations of the latter condition.

M. S. S.

[7] UNGAR, G.: Endocrine function of the spleen and its participation in the pituitary-adrenal response to stress, Endocrinology, 1945, xxxvii, 329–340.

REVIEWS

Topley and Wilson's *Principles of Bacteriology and Immunity*. By G. S. Wilson, M.D., F.R.C.P., D.P.H., K.H.P., and A. A. Miles, M.A., F.R.C.P. Third Edition. Two Volumes. 2054 pages; 16.5 × 23.5 cm. Williams and Wilkins Co., Baltimore. 1946. Price, $12.00.

This new revision of an important and comprehensive work will be welcomed by bacteriologists and others interested in infectious diseases. The general plan of presentation of the second edition has been retained. The text has, as formerly, been divided into two volumes with the index conveniently appended to both.

Volume I contains the sections on General and Systematic Bacteriology. Under General Bacteriology are discussed characteristics of bacteria, principles of disinfection, antigenic structure, the antigen-antibody reaction and bacteriophage. There is a new chapter on antibacterial substances used in the therapy of infections. Part II, after some introductory material on methods, consists of discussions by genera of the various organisms encountered in medical bacteriology. The nomenclature employed is a modified version of the American system, especially of the form set forth in the report of the committee of the Society of American Bacteriologists in 1920. A notable innovation is the recognition of the terms *Salmonella* and *Shigella* for designation of organisms previously included in the *Genus Bacterium*.

In the second volume are the sections: Infection and Resistance and The Application of Bacteriology to Medicine and Hygiene. In the latter, which is chiefly a series of chapters on specific infections, the number of virus diseases included has been greatly increased and the lymphogranuloma-psittacosis group is taken up separately. The book closes with considerations of the bacteriology of man, air, milk, and water, shellfish and sewage. The new chapter on aerobiology reviews recent developments in the disinfection of air in closed spaces. A discussion of soil bacteriology and natural economy has unfortunately been deleted.

With the exceptions noted, the changes have been minor ones—mainly the insertion of new material—so that, as a result, the edition is longer than that of 1936. The preface contains an apology for not having been more concise and some readers will agree that part of the detail might have been profitably omitted. The treatment of different subjects with respect to recent knowledge is perhaps unavoidably a little uneven. However, on the whole, the book retains its high standard of excellence and will undoubtedly be widely used both as a text and for reference work. The wealth of information and the extensive bibliographies provide a sound basis for entry into almost any line of investigation in medical bacteriology.

H. D. V.

Neurosyphilis. By H. Houston Merritt, A.B., M.A., M.D., Professor of Clinical Neurology, College of Physicians and Surgeons, Columbia University; Raymond D. Adams, M.A., M.D., Associate in Neurology, Harvard Medical School; and Harry C. Soloman, B.S., M.D., Professor of Psychiatry, Harvard Medical School. 443 pages; 24 × 16 cm. Oxford University Press, New York. 1946.

The authors adequately state the purpose of the text in their preface as follows: ". . . a text book which approached these problems from the point of view of the neurologist and the psychiatrist and at the same time critically appraised modern treatment methods." They have followed their original purpose and the final result is an excellent modern treatise on neurosyphilis. The bibliography at the end of each chapter is adequate. There are chapters dealing with fever therapy, tryparsamide, and penicillin. They have approached the individual problems by presenting the in-

dications, contraindications, advantages, and disadvantages of all methods of diagnosis and treatment. An interesting feature is the presentation of case reports throughout the text. This is a book which, in the opinion of this reviewer, should occupy a space in the library of the general practitioner and specialist.

H. M. R.

Gastro-enterology. By HENRY L. BOCKUS. Volume I. 831 pages; 25.5 × 17 cm. W. B. Saunders Company, Philadelphia. 1943. Price, $12.00.

Dr. Bockus has written a three volume work on gastro-enterology which has been hailed as a monumental contribution. The first volume which is here reviewed deals with the esophagus and stomach; Volume II with the small and large intestines and peritoneum; Volume III with the liver, biliary tract and pancreas.

The first section of Volume I deals with the examination of the patient and includes history taking, symptomatology, physical examination and laboratory examinations in gastrointestinal diseases.

Section II includes disorders of the esophagus and diaphragm with an excellent discussion of the anatomy and physiology of these structures, which introduces the pathological entities such as hiatus hernia, esophageal stricture, cardiospasm, etc. The coincidence of cardiospasm and pneumonia is properly emphasized.

Diseases of the stomach are discussed in Section III and again, a summary of the fundamental anatomy and physiology precedes the consideration of the various morbid states.

The excellent format of this book facilitates its perusal. Illustrations in the form of roentgenograms, drawings and photographs are reproduced with unusual clarity. The listings in the index are complete and orderly, increasing greatly the value of the book for reference purposes.

Dr. Bockus has successfully incorporated his own vast experience in these pages. The completed work, as judged by the quality of this first volume, will be an important addition to the literature on gastro-enterology.

J. Z. B.

BOOKS RECEIVED

Books received during September are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

X-Rays and Radium in the Treatment of Diseases of the Skin. Fourth Edition, Revised. By GEORGE M. MACKEE, M.D., and ANTHONY C. CIPOLIARO, M.D. 668 pages; 24 × 15.5 cm. 1946. Lea & Febiger, Philadelphia. Price, $10.00.

Renal Hypertension. By EDUARDO BRAUN-MENENDEZ, JUAN CARLOS FASCIOLO, LUIS F. LELOIR, JUAN M. MUNOZ, and ALBERTO C. TAQUINI, Buenos Aires. Translated by LEWIS DEXTER, M.D. 451 pages; 23.5 × 16 cm. 1946. Charles C. Thomas, Springfield, Ill. Price, $6.75.

Principles of Hematology. Third Edition, Revised. By RUSSELL L. HADEN, M.A., M.D. 366 pages; 24 × 15.5 cm. 1946. Lea & Febiger, Philadelphia. Price, $5.00.

Early Ambulation. By DANIEL J. LEITHAUSER, M.D., F.A.C.S. 232 pages; 23.5 × 16 cm. 1946. Charles C. Thomas, Springfield, Ill. Price, $4.50.

Dentistry: An Agency of Health Service. By MALCOLM WALLACE CARR, D.D.S. 219 pages; 21.5 × 14. cm. 1946. The Commonwealth Fund, New York. Price, $1.50.

Treatment of Bronchial Asthma. By VINCENT J. DERBES, M.D., and HUGO TRISTRAM ENGELHARDT, M.D., F.A.C.P. 466 pages; 24 × 16 cm. 1946. J. B. Lippincott Company, Philadelphia. Price, $8.00.

Penicillin; Its Practical Application. By multiple authors under the Editorship of Professor SIR ALEXANDER FLEMING, M.B., B.S., F.R.C.P., F.A.S. 380 pages; 22.5 × 14.5 cm. 1946. The Blakiston Company, Philadelphia. Price, $7.00.

The Drama of Sex. By JAMES LINCOLN MCCARTNEY, M.D., F.A.C.P. 147 pages; 22 × 14.5 cm. 1946. Stratford House, Inc., New York. Price, $2.50.

If You Ask My Advice. By HENRY PLEASANTS, JR., M.D. 110 pages; 21 × 14 cm. 1946. Bruce Humphries, Inc., Boston. Price, $2.00.

Environmental Warmth and Its Measurement. With 10 charts. By T. BEDFORD, D.Sc. 40 pages. British Information Services, New York. 1946.

Psychotherapy in General Practice. Report of an experimental postgraduate course. By GEDDES SMITH. 38 pages. The Commonwealth Fund. 1946. Price, .25.

COLLEGE NEWS NOTES

Reduction in the Size of the Section on College News Notes

Owing to the critical shortage of paper it will be necessary for an indeterminate period to limit the publication of College News Notes. This decision, taken at the recent meeting of the Board of Regents, has been given partial effect in the present issue, but will apply more drastically to ensuing numbers until an adequate supply of paper is once more available.

In the reduced space priority will be given to the announcements of future meetings, conferences or assemblies of special interest to internists, and to important awards to College members.

Dr. David P. Barr, F.A.C.P., President, officially represented the American College of Physicians at the meeting of the American Diabetes Association in Toronto, during September, which marked the 25th anniversary of the discovery of insulin.

The Forty-third Annual Congress on Medical Education and Licensure will meet February 10 and 11, 1947, at the Palmer House, Chicago.

Dr. F. M. Pottenger Again Honored

Dr. Frank M. Pottenger, F.A.C.P., Monrovia, Calif., former President and for many years a Regent of the American College of Physicians, was tendered a great birthday party by more than three hundred friends and former patients at the Pottenger Sanatorium and Clinic, on September 22, although his 77th birthday did not occur until September 27. Former patients came from far and near to pay tribute. Dr. Pottenger founded the Sanatorium in 1903, and during the interim more than 6,000 patients have been treated there.

The appointment of Dr. Howard A. Rusk, F.A.C.P., New York, to head the new Department of Rehabilitation and Physical Medicine of the New York University College of Medicine, has been announced. In addition to instructing medical students in problems and technics in this field, the department will coöperate with hospital authorities of New York City in establishing and supervising programs for the rehabilitation of patients in all of the city hospitals.

Dr. Rusk established the rehabilitation program of the Army Air Forces in 1942; upon this program were patterned those of the Army Service Forces, the Navy, the U. S. Public Health Service and the Veterans Administration. Dr. Rusk will continue his activities as Associate Editor of the New York Times, and consultant to the Medical Director of the Veterans Administration.

Rear Admiral John Harper, (MC), USN, F.A.C.P., Washington, D. C., has been awarded the Legion of Merit, "for exceptionally meritorious conduct in the performance of outstanding services in the planning, development and establishment of the United States Naval Hospital, National Naval Medical Center, Bethesda, Md., from the outbreak of hostilities until Feb. 4, 1942, and as medical officer in command of this hospital from Feb. 5, 1942 to April 12, 1945."

Dr. Paul R. Hawley, F.A.C.P., Chief Medical Director of the Veterans Administration, recently announced the appointment of Dr. Samuel M. Bittinger, F.A.C.P.,

Sanatorium, N. C., as Chief of Section, Tuberculosis Unit, VA Hospital, Oteen, N. C.; Dr. George C. Wilson, F.A.C.P., Wallingford, Conn., as Assistant Chief, Tuberculosis Section, VA Branch Office No. 1, Boston; Dr. Morris C. Thomas (Associate), Indianapolis, as Chief of Section, Tuberculosis Unit, VA Hospital, Dayton, Ohio.

The appointments of 18 Fellows and two Associates of the College to be civilian consultants to the Secretary of War, through the Surgeon General, were recently announced. These were as follows:

Internal medicine: Dr. Arthur C. Curtis, F.A.C.P., Ann Arbor, Mich.; Dr. Francis R. Dieuaide, F.A.C.P., New York; Dr. Garfield G. Duncan, F.A.C.P., Philadelphia; Dr. Edgar Durbin, F.A.C.P., Denver; Dr. Lester C. Feener (Associate), El Paso, Tex.; Dr. Harry T. Harper, Jr., F.A.C.P., Augusta, Ga.; Dr. William J. Kerr, F.A.C.P., San Francisco; Dr. Orlando B. Mayer, F.A.C.P., Columbia, S. C.; Dr. John B. McKee, F.A.C.P., Winchester, Va.; Dr. William S. Middleton, F.A.C.P., Madison, Wis.; Drs. Samuel Morrison, F.A.C.P., and Maurice C. Pincoffs, F.A.C.P., Baltimore; Dr. Monroe J. Romansky (Associate), Silver Spring, Md.; Dr. S. Marion Salley, F.A.C.P., Miami, Fla.; Dr. James J. Waring, F.A.C.P., Denver; Dr. Wallace M. Yater, F.A.C.P., Washington, D. C.

Neuropsychiatry: Dr. Hervey M. Cleckley, F.A.C.P., Augusta, Ga.; Dr. Walter Freeman, F.A.C.P., Washington, D. C.

X-Ray: Dr. Arthur C. Christie, F.A.C.P., Washington, D. C.

Radiology: Dr. Edgar M. McPeak, F.A.C.P., Washington, D.C.

At its meeting in New York the first week in September, the American Congress of Physical Medicine awarded Dr. Ralph Pemberton, F.A.C.P., Philadelphia, the Distinguished Service Gold Key for outstanding accomplishments in the field.

Colonel James E. Ash, (MC), USA, F.A.C.P., Washington, D. C., Director of the Army Institute of Pathology, received the following tribute from the American Society of Clinical Pathologists: "The Army Institute of Pathology has contributed immeasurably to the increasing knowledge in the medical field, particularly that of pathology, and has reflected credit on the Army Medical Department and the United States Army, and has fostered a military-civilian liaison that was nothing short of priceless in World War II. The leadership for these far reaching projects was from 1937 to the present vested in Colonel James E. Ash from whose inspiration, judgment and scientific acumen stemmed the success of many of these projects."

Dr. Howard F. West, F.A.C.P., Los Angeles, President of the American Heart Association, Inc., has designated February 9–15, 1947, as National Heart Week. During this week the educational activities of the Association, which emphasize the importance of rheumatic fever and heart disease in children, will reach a climax. The American College of Physicians is supporting and coöperating in the work of the American Council on Rheumatic Fever of the Association.

The National Gastroenterological Association at its Annual Convention Banquet, June 1947, will award $100 and a certificate of merit for the best unpublished contribution on gastroenterology or allied subjects in its 1947 Award Contest. Additional certificates will be awarded to worthy, but less meritorious, contributions. Contestants must be members of the American Medical Association or similar organizations in other countries. The Association reserves exclusive right to publish the honored con-

tributions in The Review of Gastroenterology. Entries should be limited to 5,000 words, typewritten in English in manuscript form, and submitted not later than April 1, 1947, accompanied by an entry letter, to the Association, 1819 Broadway, New York 23, N. Y.

The appointment of Dr. John B. Youmans, F.A.C.P., Nashville, Tenn., to the Deanship of the University of Illinois College of Medicine was recently announced. Dr. Youmans is presently Professor of Medicine and Acting Dean of the Vanderbilt University School of Medicine. He graduated in 1919 from the Johns Hopkins University School of Medicine, became a Fellow of the College in 1925, and is a diplomate of the American Board of Internal Medicine. Dr. Youmans served during 1940–41 as a member of the Rockefeller Foundation Health Commission to Europe. He is a Fellow of the American Medical Association, and a member of the Southern Medical Association, American Society for Clinical Investigation, American Clinical and Climatological Association, and of the Association of American Physicians.

Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., recently received the Distinguished Service Award for 1946 of the Mississippi Valley Medical Society, "in recognition of unusual and distinguished services as editor, as administrator and as founder of medical periodicals and societies, of a medical library and of endowment funds and a foundation, all of them designed to help physicians in private practice to continue their education; to stimulate clinical research; to promote good fellowship and advance the interests of the members of the profession; and to make more readily available, especially in rural and urban areas, a higher quality of medical service; and in appreciation of his zealous and untiring efforts in behalf of the Society and its members."

The series of Friday Afternoon Lectures of the New York Academy of Medicine, 1946–47, will include the following by Fellows of the College:

December 6, Dr. Z. Taylor Bercovitz, New York, "Colitis."
January 3, Dr. A. J. Carlson, Chicago, "The Treatment of Chronic Alcoholism by the General Practitioner."
March 28, Dr. Lloyd F. Craver, New York, "Recent Advances in the Treatment of Lymphomas and Leukemias."

Dr. Francis J. Braceland, F.A.C.P., has retired from active duty in the U. S. Naval Reserve, where he had the rank of Captain, and is now Consulting Psychiatrist to the Mayo Clinic and Professor of Psychiatry, Mayo Foundation, University of Minnesota Graduate School.

Dr. John Q. Griffith, Jr., F.A.C.P., Philadelphia, Pa., Dr. M. August Lindauer (Associate), Philadelphia, Pa., Dr. Ralph L. Shanno, F.A.C.P., Forty Fort, Pa., and Dr. James F. Couch, Eastern Research Laboratory of the U. S. Department of Agriculture, were awarded a Certificate of Merit by the American Medical Association at the San Francisco meeting for an exhibit entitled "Rutin: Treatment for Hypertension Associated with Increased Capillary Fragility."

Dr. Ralph L. Shanno, F.A.C.P., Forty Fort, Pa., Dr. John Q. Griffith, Jr., F.A.C.P., Philadelphia, Pa., and Dr. William LaMotte, Jr., Philadelphia, Pa., received an award for a scientific exhibit at the Philadelphia meeting of the Medical Society of the State of Pennsylvania, held during October, 1946, for an exhibit entitled "Capillary Fragility and Capillary Permeability in Relation to Retinal Hemorrhage."

Emory University Offers Informal Courses of Postgraduate Type

Dr. Russell H. Oppenheimer, F.A.C.P., Professor of Clinical Medicine at Emory University, Atlanta, Ga., has recently announced that the University will offer informal courses of instruction of a postgraduate type to men in practice. These are arranged for varying periods of time, preferably for a three months or quarter basis. They will, however, take students for periods as short as two weeks.

At the Fortieth Annual Meeting of the Southern Medical Association, which occurred November 4–7, at Miami, Fla., Dr. William H. Sebrell, Jr., F.A.C.P., Bethesda, Md., was presented with the Association's Research Medal for his studies on nutrition in relation to public health.

The Canadian Medical Procurement and Assignment Board published a very valuable guide for medical officers retiring from active duty. The pamphlet is entitled, "Facts about Your Medical Career on Demobilization." The publication gives detailed information concerning the advantages and opportunities to which retiring medical officers are eligible. It reviews in some detail the matter of refresher courses, postgraduate training, placement, and miscellaneous appointments. It contains a complete survey of medical refresher courses, internships, residencies, assistantships, fellowships, etc.

Copies are available through the Canadian Medical Association, 184 College St., Toronto, or through the headquarters of the Board at Ottawa.

Dr. Abraham M. Kleinman (Associate), Brooklyn, N. Y., has been awarded the Army Commendation Ribbon in recognition of his services as Assistant Chief and Chief of Medical Service at Halloran General Hospital, Staten Island, N. Y.

American College of Physicians Regional Meetings

North Carolina

Under the Governorship of Dr. Paul F. Whitaker, F.A.C.P., Kinston, a Regional Meeting of the College for North Carolina took place October 18, at Winston-Salem. The scientific program was as follows: The Diagnosis and Treatment of Rheumatoid Spondylitis, Dr. Richard Z. Query, Jr., F.A.C.P., Charlotte, N. C.; The Technic and Value of Therapeutic Pneumoperitoneum, Dr. Joseph S. Hiatt, Jr. (Associate), Sanatorium, N. C.; Cecal Granulomata, Dr. Charles M. Caravati, F.A.C.P., Richmond, Va.; Surgery of Patent Ductus Arteriosus (Moving pictures), Dr. Howard H. Bradshaw, Winston-Salem, N. C.; Clinico-Pathological Conference, Drs. Oscar E. Hansen-Pruss, Durham, N. C. and Robert P. Morehead, F.A.C.P., Winston-Salem, N. C.

An informal dinner at the Old Town Club followed the scientific sessions. The guest address was delivered by Dr. Leslie B. Hohman, Visiting Professor of Psychiatry, Duke University. Dr. Whitaker also spoke at the dinner.

North Central States

A Regional Meeting of the College for the states of Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota and Wisconsin, occurred at Chicago, November 16. Dr. Walter L. Palmer, Governor for Northern Illinois, served as Chairman of the Local Program Committee. Drs. Douglas Donald, Cecil M. Jack, Robert M. Moore, Karver L. Puestow, and B. F. Wolverton, Governors for Michigan, Southern Illinois, Indiana, Wisconsin, and Iowa, respectively, presided at the meetings. Dr. Andrew C.

Ivy, F.A.C.P., Vice President and Distinguished Professor of Physiology, University of Illinois, spoke at the evening session on the topic, "War Crimes of a Medical Nature." Dr. David P. Barr, President, Dr. Chauncey W. Dowden, Chairman of the Board of Governors, Dr. Morris Fishbein, Editor of the Journal of the American Medical Association, Dr. Ernest E. Irons, Past President and Regent, Mr. Edward R. Loveland, Executive Secretary, and Dr. LeRoy Sloan, Regent and General Chairman of the 1947 Annual Convention, also addressed remarks following the dinner at which Dr. E. V. Allen, Governor for Minnesota, was Toastmaster. The scientific program was as follows: Peritoneoscopy: Clinical and Pathological Correlations in Epidemic Hepatitis, Dr. Thomas N. Horan, F.A.C.P., Detroit; Early Diagnosis and Treatment of Subclinical Liver Impairment, Dr. John G. Mateer, F.A.C.P., Detroit; Homologous Serum Jaundice, Dr. Richard B. Capps, F.A.C.P., Chicago; Amebic Hepatitis, Dr. George W. Pedigo, F.A.C.P., Louisville; Antibody Relationships of Blood Plasma Protein, Dr. Harold Duetsch, Madison; Amino Acids in Nephrosis, Dr. Douglas A. MacFagden, Chicago; The Role of Amino Acids in Nutrition, Dr. W. C. Rose, Urbana, Ill.; The Metabolism of Chiniofon, Drs. Edgar S. Gordon, F.A.C.P., and E. C. Albright, Madison, Wis.; Transport and Excretion of Uric Acid In Normal and Gouty Individuals, Drs. R. Levine and William Q. Wolfson, Chicago; The Use of Diet in the Management of Calcium Phosphate Urolithiasis, Dr. R. H. Flocks, F.A.C.S., Iowa City; Extra Renal Uremia, Dr. Francis D. Murphy, F.A.C.P., Milwaukee; Thiouracil in the Treatment of Hyperthyroidism, Dr. J. O. Ritchey, F.A.C.P., Indianapolis; End Results of Treatment of Pituitary Dwarfism with Sex Hormones, Dr. Willard O. Thompson, F.A.C.P., Chicago; Chemotherapy and Radioactive Substances in the Treatment of Diseases of the Hemopoietic System, Dr. Leon O. Jacobson, Chicago; Surgical Treatment of Hypertension, Dr. Adrien Verbrugghen, F.A.C.S., Chicago; Pulmonary Adenomatosis, Dr. Frederick J. Pohle, Madison; Neurologic Causes of Pain in the Upper Extremities, Dr. Lee M. Eaton, Rochester, Minn.; Management of Patients with Cardiospasm, Dr. Frank R. Peterson, F.A.C.S., Iowa City; Clinical Manifestations of Alkalosis, Dr. David P. Barr, F.A.C.P., New York; Vascular Emergencies, Dr. E. A. Hines, Jr., F.A.C.P., Rochester, Minn.; Present Status of Folic Acid in the Treatment of Macrocytic Anemia, Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor; Isolated Myocarditis, Dr. O. Saphir, Chicago; Disseminated Inflammatory Lesions Following Sulfonamide Administration, Dr. Eleanor M. Humphreys, Chicago; Present Status of Treatment of Bacterial Endocarditis With Penicillin, Dr. C. Phillip Miller, F.A.C.P., Chicago; Penicillin Therapy of Syphilis, Dr. J. Murray Kinsman, Louisville; Clinical Use of Streptomycin, Dr. Wallace E. Herrell, F.A.C.P., Rochester, Minn.; Present Status of the Scarlet Fever Problem, Dr. Paul S. Rhoads, F.A.C.P., Chicago; Clinical Intoxication with Potassium, Dr. Norman M. Keith, Rochester, Minn.; Cor Pulmonale: A Comparison of the Acute and Chronic Forms, Dr. Norbert Enzer, F.A.C.P., Milwaukee.

Florida

Preceding the meetings of the Southern Medical Association, a Regional Meeting of the College occurred at Miami Beach, Fla., November 3 and 4, through the cooperation of Dr. Turner Z. Cason, F.A.C.P., Jacksonville, Dr. Glenville Giddings, F.A.C.P., Atlanta, Dr. E. Dice Lineberry, F.A.C.P., Birmingham, and Dr. Kenneth M. Lynch, F.A.C.P., Charleston, College Governors for Florida, Georgia, Alabama and South Carolina, respectively. Dr. Edward L. Bortz, F.A.C.P., Philadelphia, Vice-Chairman of the Board of Governors and Chairman of the Advisory Committee on Postgraduate Courses, and the visiting Governors were guest speakers at the Luncheon Meeting at the McAllister Hotel, November 4. The scientific program consisted of the following: Chronic Cor Pulmonale: Case Due to Pulmonary Artery Compression by Aneurysm of Aorta, Dr. Julius R. Pearson, F.A.C.P., Miami Beach; Climate and

Heart Disease, Dr. Herbert Eichert (Associate), Miami; Delayed Convalescence in Infectious Hepatitis, Dr. Donald F. Marion, F.A.C.P., Miami; Value and Limitations of X-ray Study of the Gastrointestinal Tract, Dr. Frederick K. Herpel, F.A.C.P., West Palm Beach; Clinic: Treatment of Cirrhosis of Liver, Dr. Franz Stewart, F.A.C.P., Miami; Clinic: Demonstration of Cardiac Cases, Drs. Charles F. Roche, F.A.C.P., and Donald F. Stannus (Associate), Miami Beach.

Western Michigan Regional Meeting of the College, Grand Rapids

A Regional Meeting of the members of the American College of Physicians was held at Grand Rapids, October 30, 1946, under the chairmanship of Dr. Burton R. Corbus, F.A.C.P. The program was as follows: Bacterial Endocarditis, Dr. J. D. Venema—Discussant, Dr. L. Paul Ralph (Associate); A Group of Interesting and Unusual Arthritides, Dr. Carl B. Beeman, F.A.C.P., Grand Rapids—Discussant, Dr. William D. Robinson, F.A.C.P., Ann Arbor; Echinococcus Disease of the Lungs, Dr. Noyes L. Avery, Jr. (Associate), Ann Arbor—Surgical discussant, Dr. J. Duane Miller, F.A.C.S., Grand Rapids; Undulant Fever, Dr. Gordon W. Balyeat, F.A.C.P., Grand Rapids; Cutaneous Lymphosarcoma, Dr. Ralph L. Fitts, F.A.C.P., Grand Rapids; Social Hour; Dinner.

Guest Speaker at the dinner given at the University Club was Dr. D. Robinson. His topic was "Some Observations on Malnutrition as It Actually Occurs in Population Groups."

Corrections

In College News Notes, September 1946, page 550, the service designation USN and the address, Philadelphia, were ascribed to Dr. George Cupp Griffith, F.A.C.P. Dr. Griffith served in the Medical Corps of the Naval Reserve, and is located in Los Angeles.

In the College News Notes, August, 1946, page 389, it was incorrectly stated that "Dr. Joseph S. Hiatt, F.A.C.P., Sanatorium, N. C., has been appointed to the position of Superintendent of the Hugh Chatham Memorial Hospital, Elkin, N. C." Dr. Joseph S. Hiatt, Jr. (Associate), has in fact been appointed to the position of Associate Superintendent and Associate Medical Director of the North Carolina Sanatorium for the Treatment of Tuberculosis, Sanatorium, N. C.; Dr. Hiatt's father, the Reverend J. D. Hiatt, D. D., has been appointed Superintendent of the Hugh Chatham Memorial Hospital.

Gifts to the College Library

Dr. Ralph Bowen, F.A.C.P., Houston, Tex.—3 reprints
Dr. Charles H. Lutterloh, F.A.C.P., Hot Springs National Park, Ark.—1 reprint
Dr. Fred M. Meixner, F.A.C.P., Peoria, Ill.—5 reprints
Dr. Bradford Murphey, F.A.C.P., Denver, Col.—1 reprint
Dr. D. E. Nolan (Associate), Dayton, Ohio—3 reprints
Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—1 reprint
Dr. Joseph T. Roberts (Associate), Washington, D. C.—1 reprint
Dr. Carl F. Shaffer (Associate), Houston, Tex.—6 reprints
Dr. Edward J. Stieglitz, F.A.C.P., Washington, D. C.—6 reprints
Dr. John Mumford Swan, F.A.C.P., Rochester, N. Y.—4 reprints
Dr. Charles C. Verstandig (Associate), New Haven, Conn.—1 reprint
Dr. R. Lomax Wells, F.A.C.P., Washington, D. C.—1 reprint

The College acknowledges with thanks to the author, Dr. Edward R. Janjigian (Associate), Edinburg, Ind., a copy of his novel, entitled "Doctor Destiny," which has been added to the College Library.

Retirements from Service

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to October 12, 1946 inclusive).

Frank M. Adams, Hot Springs National Park, Ark. (Lt. Col., MC, AUS)
Charles H. Armentrout, Asheville, N. C. (Lt. Comdr., MC, USNR)
Robert E. Driscoll, Chicago, Ill. (Capt., MC, AUS)
Albert M. Eaddy, Columbia, S. C. (Major, MC, AUS)
Angelo S. Geraci, Chicago, Ill. (Major, MC, AUS)
Mack L. Gottlieb, New York, N. Y. (Comdr., MC, USNR)
Albert S. Hyman, New York, N. Y. (Capt., MC, USNR)
Clyde H. Kelchner, Allentown, Pa. (Major, MC, AUS)
Norman Learner, Philadelphia, Pa. (Major, MC, AUS)
Harris V. Lilga, Petoskey, Mich. (Major, MC, AUS)
Murlin P. Merryman, Rapid City, S. D. (Major, MC, AUS)
William C. Munly, Portland, Ore. (Col., MC, USA)
Frazier J. Payton, Miami Beach, Fla. (Comdr., MC, USNR)
Heyes Peterson, Wheeling, W. Va. (Lt., MC, USNR)
Wilfrid E. Riddolls, Brantford, Ont., Can. (Lt. Col., RCAMC)
Elmer S. Robertson, Richmond, Va. (Major, MC, AUS)
Robert B. Rutherford, Peoria, Ill. (Col., MC, AUS)
George C. Thomas, Chevy Chase, Md. (Rear Admiral, MC, USN)
Ray Vander Meer, Grand Rapids, Mich. (Major, MC, AUS)
Samuel J. Weinberg, Los Angeles, Calif. (Major, MC, AUS)
Jack Wexler, Boston, Mass. (Major, MC, AUS)
Andrew Yeomans, Baltimore, Md. (Comdr., MC, USNR)

Elections to Membership, American College of Physicians

On October 20, 1946, on the recommendation of the Committee on Credentials, the Board of Regents formally elected the following candidates to membership. (73 FELLOWS, indicated in full CAPITALS; 126 Associates, indicated in lower case).

Abels, Jules C., New York, N. Y.
ALLEN, IRENE VIOLA, East St. John, New Brunswick, Can.
Anday, George John, Chicago, Ill.
Anthony, Eleanor Margaret, Philadelphia, Pa.

ARNETT, SAMUEL CULLEN, JR., Lubbock, Tex.
Avey, Harry Thompson, Jr., Oklahoma City, Okla.
Balberor, Harry, Detroit, Mich.
BARTON, EVAN MANSFIELD, Chicago, Ill.
Bass, Hyman Elihu, New York, N. Y.
Bates, Clarence Edgar, Oklahoma City, Okla.
BERNSTEIN, ARTHUR, Chicago, Ill.
BEST, GORDEN NEWALL, Council Bluffs, Iowa
Beyer, Karl Henry, Jr., Bala-Cynwyd, Pa.
Blumenthal, Basil, Washington, D. C.
Boger, William Pierce, Philadelphia, Pa.
BOLAND, EDWARD WARD, Los Angeles, Calif.
Boone, Leslie Jay, Washington, Pa.
Borson, Harry J., Berkeley, Calif.
Bosworth, Edward Louis, Rome, Ga.

Branch, Charles Henry Hardin, Philadelphia, Pa.
Brandsma, Maynard, Beverly Hills, Calif.
Branning, William Sterry, Durham, N. C.
Brightman, I. Jay, Albany, N. Y.
Brooks, Nathan, Detroit, Mich.
BROSIN, HENRY WALTER, Chicago, Ill.
Brown, Jesse Benjamin, Ancon, C. Z.
Budnitz, Joseph, Pittsfield, Mass.
BUTLER, STUYVESANT, Winnetka, Ill.

CANDEL, SAMUEL, Brooklyn, N. Y.
CARROLL, HOWARD BERTRAM, Chicago, Ill.
Chanis, Rolando Augusto, Panama, R. P.
Chatard, Ferdinand Edme, (MC), USN, Washington, D. C.
Cherry, Clifford Burns, Los Angeles, Calif.
Christman, Herbert Emanuel, Lakewood, Ohio
Closterman, Donald Franks, Kingston, Pa.
COGGESHALL, LOWELL THELWELL, Chicago, Ill.
Colvin, Merl G., Williamsport, Pa.
Corrado, Albert Guy, Pittsburgh, Pa.
Cotter, Edward Francis, Baltimore, Md.
CRAGO, FELIX HUGHES, Great Falls, Mont.
CRAIN, DARRELL CLAYTON, Washington, D. C.
Crumrine, Clarence Acklin, Washington, Pa.

Danowski, Thaddeus Stanley, New Haven, Conn.
DAVIS, JOHN PRESTON, Winston-Salem, N. C.
Dick, Macdonald, Durham, N. C.
Dobson, Herbert Victor, Peterborough, Ont., Can.
Doty, Edwin John, New York, N. Y.
DUNN, THOMAS BALFOUR, Oakland, Calif.
DUNN, WILLIAM LeROY, Washington, D. C.

ECHIKSON, JOSEPH ISRAEL, Newark, N. J.
ENGLISH, JOHN PAUL, South Bend, Ind.
Evans, Carvel Swift, Salt Lake City, Utah
EVANS, ELWYN, Winter Park, Fla.

Fairchild, Laurence McCarty, Ancon, C. Z.
FISHER, H(ARRY) RUSSELL, Bala-Cynwyd, Pa.
Fisher, Saul H., New York, N. Y.
Florio, Lloyd Joseph, Denver, Colo.
Ford, Elbert Sylvester Caldwell, Philadelphia, Pa.
Forte, Joseph Anthony, Jr., (MC), USN, Washington, D. C.
Fox, Theodore T., New York, N. Y.
Freeman, Joseph, Philadelphia, Pa.
Freireich, Kal, Forest Hills, N. Y.
FRENCH, A(DAM) JAMES, Ann Arbor, Mich.
Friedman, Gerald Jonas, New York, N. Y.

Gendel, Benjamin Robert, New Haven, Conn.
GETTELFINGER, WILFRID CHARLES, Louisville, Ky.
GILL, CHARLES CHUTE, (MC), USA, Washington, D. C.

Gillick, Frederick George, Willow Grove, Pa.
GILMAN, ROBERT LOUIS, Wallingford, Pa., (MC), USNR
Goldhamer, Morton Louis, Cleveland, Ohio
GRAHAM, ROBERT WILLIAMS, Toronto, Ontario, Can.
Greenberg, Samuel U., New York, N. Y.
GUTHRIE, MORRIS BAKER, Columbus, Ohio

Hammel, Max Arthur, Santa Barbara, Calif.
Hartnett, William Gordon, Muskogee, Okla.
Harvey, Joseph Paul, Youngstown, Ohio
HAYS, JAMES FRANKLIN, (MC), USN, Washington, D. C.
Henry, Blondy Sewell, Memphis, Tenn.
HERNANDEZ, VINCENT, (MC), USN, Washington, D. C.
Hilker, Albert William, Eau Claire, Wis.
HOLLANDER, JOSEPH LEE, Philadelphia, Pa.
HOLMAN, CHARLES NIXON, Portland, Ore.
Horwitz, Orville, Philadelphia, Pa.

IRVINE, JED HOTCHKISS, New York, N. Y.
Issos, Demetrios Nestor, Birmingham, Ala.
Jenkins, Daniel Edwards, Ann Arbor, Mich.
JENNINGS, HARRY NELSON, Calgary, Alberta, Can.
Johnson, Carl Harold, Gettysburg, Pa.
Josephs, Irving Louis, Los Angeles, Calif.
Joslyn, Harold Lees, St. Louis, Mo.

Kapp, Louis A., New York, N. Y.
Kaufman, Paul, New York, N. Y.
KEENEY, EDMUND LUDLOW, Baltimore, Md.
KENNEDY, J(AMES) ALLEN, Nashville, Tenn.
Keyes, John Wesley, Detroit, Mich., (MC), AUS
KLEEFIELD, ELMER ALFRED, Forest Hills, N. Y.
KNEEDLER, WILLIAM HARDING, Philadelphia, Pa.
Kohl, Harold Willis, Tucson, Ariz.
Kostal, Otto Albin, Hastings, Nebr.
KUBANEK, JOSEPH LOUIS, Eloise, Mich.
KWITNY, ISADORE JACOB, Indianapolis, Ind.

LaDUE, JOHN SAMUEL, New York, N. Y.
LANDAU, FREDERICK LOUIS, JR., Bronxville, N. Y.
Langendorf, Richard, Chicago, Ill.
Layman, Leslie Holmes, Louisville, Ky.
LEGER, LEE HERMAN, Kansas City, Kan.
LEHNHOFF, HENRY JOHN, JR., Omaha, Nebr.
Leming, Howell Elijah, Fayetteville, Ark.
LEONARD, CHARLES EDWARDS, Oklahoma City, Okla.
Livingston, A. Edward, Bloomington, Ill.

Magee, Conway Stone, Lake Charles, La.
Mallach, Joseph Francis, Chicago, Ill.
MANNING, ISAAC HALL, JR., Durham, N. C.
Mattingly, Thomas William, (MC), USA, Washington, D. C.
McCombs, (Annie) Parks, New York, N. Y.

Mensh, Maurice, Washington, D. C.
Miller, Edward Bernard, New York, N. Y.
Miller, Harry Irwin, Pittsburgh, Pa.
MODELL, WALTER, New York, N. Y.
Montgomery, Max Malcolm, Chicago, Ill.
Moore, Matthew Thibaud, Philadelphia, Pa.
MURPHY, PAUL, St. Louis, Mo.
Musser, Marc James, Jr., Madison, Wis.

Nayer, Herman R., New York, N. Y.
Nelson, James David, Spartanburg, S. C.
Nelson, Oscar Louis Norman, Minneapolis, Minn.
NICHOLSON, WILLIAM McNEAL, Durham, N. C.

Oren, Benjamin Gershwin, Miami, Fla.

PETERS, GUSTAVUS ALFRED, Rochester, Minn., (MC), AUS
PETERS, MICHAEL, Telford, Pa.
Phelps, James Everett, Paterson, N. J.
Pohle, Frederick John, Madison, Wis.
Province, William Ditmars, Franklin, Ind.

Redisch, Walter, Jackson Heights, N. Y.
Reifenstein, George Henry, Syracuse, N. Y.
Reitman, Norman, New Brunswick, N. J.
Rivers, Daniel Christopher, Cincinnati, Ohio
Robins, Arthur Benjamin, New York, N. Y.
Robinson, Murry Myer, Washington, D. C.
ROPER, WILLIAM HAMILTON, Sanatorium, N. C., (MC), AUS
Rosenkrantz, Jacob Alvin, New York, N. Y.
ROTKOW, MAURICE JULIAN, Des Moines, Iowa
RUSKIN, ARTHUR, Galveston, Tex.

SAPERO, JAMES JOSEPH, (MC), USN, Washington, D. C.
SCARLETT, EARLE PARKHILL, Calgary, Alberta, Can.
Schoemperlen, Clarence Benjamin, Winnipeg, Manitoba, Can.
Schwade, Edward David, Milwaukee, Wis.
SCHWARTZ, WALTER HENRY, (MC), USN, Washington, D. C.
SENECA, HARRY TUNE A., New Orleans, La.
SHAFFER, CARL FRANCIS, Houston, Tex.
Shapiro, Herman Harvey, Madison, Wis.
Sharp, Reuben Lore, Camden, N. J.
Shuey, Charles B., Dallas, Tex.
Sikkema, Stella Hazen, Madison, Wis.
Silbermann, Isador, New York, N. Y.
Simonart, Pierre Charles, Philadelphia, Pa.
Sims, John LeRoy, Madison, Wis.
SKINNER, ROBERT BARRETT, (MC), USA, Washington, D. C.
Sloan, Norman Rose, Kalaupapa, Molokai, T. H.
Smith, Jasper Archer, Waterbury, Conn.
SMITH, JEROME FROST, (MC), USN, Washington, D. C.
Smith, Sol(omon), Baltimore, Md.
SOLEM, GEORGE OLIVER, Chicago, Ill.

Sorkin, S. Zelig, New York, N. Y.
STARR, (MERRITT) PAUL, Pasadena, Calif.
Steinberg, David Louis, Elgin, Ill.
Stellar, Lawrence Irving, Boston, Mass.
Stewart, Donald William Wright, Sudbury, Ontario, Can.
STEWART, WILLIAM CRAWFORD, Charleston, W. Va.
STONE, CHARLES FREDERIC, JR., Atlanta, Ga.
Stone, Frederick James, Buffalo, N. Y.
Sullivan, Clement Joseph, St. Louis, Mo.
SUNDERMAN, F(REDERICK) WILLIAM, Philadelphia, Pa.

Taylor, William Wood, Memphis, Tenn.
Thomas, Caroline Bedell, Baltimore, Md.
Thomas, Sydney Frissell, Menlo Park, Calif.
Thompson, James Harwood, San Francisco, Calif.
Thompson, William Taliaferro, Jr., Richmond, Va.
Tracey, Martin L., Needham, Mass.
Trawick, John David, Jr., Louisville, Ky.

VOEGTLIN, WALTER LYLE, Seattle, Wash.

WAKEMAN, DON CONKLIN, Topeka, Kan.
Warburton, Ralph Thomas, North Canton, Ohio
WARRICK, GEORGE WILKS, Birmingham, Ala.
WARSHAWSKY, HARRY, Dayton, Ohio
Weiner, Joseph G., Philadelphia, Pa.
WHITE, ARTHUR EUGENE, (MC), USA, Washington, D. C.
WHITE, ASHER ABBOTT, Minneapolis, Minn.
WHITE, MAJOR SAMUEL, (MC), USA, Washington, D. C.
WILLETT, FORREST MUNROE, San Francisco, Calif.
Williams, Leonard David, Plainfield, N. J.
WILSON, CHARLES PEARSON, Portland, Ore.
Wilson, Joseph McMilton, Dayton, Ohio
Wilson, Rex Hamilton, Akron, Ohio
Wirts, Charles Wilmer, Jr., Philadelphia, Pa.
Wolfman, Benjamin H., USPHS, Washington, D. C.
Wolpaw, Ralph, Cleveland, Ohio

Yarmy, Milton Marvin, Youngstown, Ohio

Zolov, Benjamin, Portland, Maine

James A. Halsted, M.D., F.A.C.P., has been appointed Chief of the Medical Service of the Faulkner Hospital, Jamaica Plain, Boston, to succeed Channing Frothingham, M.D., F.A.C.P., who has reached the retiring age.

Dr. Halsted is a graduate of the Harvard Medical School and received his intern and resident training at the Massachusetts General Hospital and the Lakeside Hospital in Cleveland. He is a diplomate of the American Board of Internal Medicine and a member of the American College of Physicians. He holds the rank of Assistant Physician at the Massachusetts General Hospital. Dr. Halsted was overseas with the 6th General Hospital and on his discharge held the rank of Lieutenant Colonel. He was awarded the Legion of Merit. Dr. Halsted practices internal medicine in Dedham.

OBITUARIES

DR. WILLIAM SCHAEFFER BERTOLET

William Schaeffer Bertolet, M.D., F.A.C.P., was born in Oley, Berks County, Pennsylvania, in 1875. He attended Keystone State Normal School at Kutztown, and Franklin and Marshall College of Lancaster. He graduated from the University of Pennsylvania School of Medicine in 1900. At one time he was assistant to the late Dr. Judson Daland, F.A.C.P., of Philadelphia. For several years he was Pathologist at the Reading Hospital, thereafter becoming Chief of the Medical Service and Medical Director. He was formerly President of the Berks County Medical Society; a member of the Reading Medical Society, the Pennsylvania State Medical Society, the American Medical Association; a Fellow of the American College of Physicians since 1923; and a Diplomate, American Board of Internal Medicine.

Dr. Bertolet was one of the leaders in the field of Internal Medicine in the Eastern part of Pennsylvania. He died on October 9, 1946. His passing will be mourned by a large number of patients and a wide circle of distinguished friends.

E. L. Bortz, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. MATHEW ARNOLD SPANGELBERGER

Mathew Arnold Spangelberger, M.D., F.A.C.P., was born in New Albany, Indiana, in 1880, where he lived until entering the University of Louisville for his premedical training. After graduation with the M.D. degree from the Denver and Gross College of Medicine in 1904, he began practice in Denver and continued active until shortly before his death on June 9, 1946, at the age of 66.

Dr. Spangelberger was a prominent figure in Colorado Medicine throughout his active professional life. He was particularly active as a consultant in Internal Medicine upon the staff of Saint Anthony's Hospital, twice serving as president. He also held appointments upon the staffs of St. Luke's, Children's, St. Joseph's, Denver General and Mercy Hospitals. He was director for many years of the diagnostic division of the Ave Maria Clinic, and in spite of failing health he assumed heavy war-time teaching duties in the Outpatient Department of the University of Colorado School of Medicine. Dr. Spangelberger spent frequent periods in postgraduate study at such institutions as the Harvard, Northwestern, Chicago Postgraduate, and New York Postgraduate Medical Schools. He was a member of the Denver County and Colorado State Medical Societies, the American Heart Asso-

ciation and a Fellow of the American Medical Association and the American College of Physicians, the latter since 1931.

WARD DARLEY, M.D., F.A.C.P.,
Governor for Colorado

DR. JOSEPH E. SCOTT

Joseph Eckles Scott, M.D., F.A.C.P., died in Portland, Oregon, on April 23, 1946, at the age of 32. Dr. Scott was born on October 14, 1913, in Portland. He graduated from Willamette University in Salem with a B.A. degree in 1935. Following this he entered the University of Oregon Medical School, receiving the M.A. degree in Biochemistry in 1937 and the M.D. degree in 1941. He was a member of Sigma Xi and Alpha Omega Alpha. He completed an internship in 1942 and served a residency in Medicine at the University of Oregon Medical School Hospitals and Clinics from July 1, 1942 to December 31, 1943.

Dr. Scott was associated with Dr. Blair Holcomb in the practice of medicine until he entered practice by himself in November, 1945. He was an Instructor in Medicine at the University of Oregon Medical School and a member of the staff of Good Samaritan Hospital.

Dr. Scott was highly respected by the medical profession and his loss will be keenly felt.

D. W. E. BAIRD, M.D., F.A.C.P.

DR. CHAMPNEYS HOLT HOLMES

Dr. Champneys Holt Holmes, 52, a Fellow of the American College of Physicians since 1937, died June 12, 1946, in a private hospital in Jacksonville, Florida.

Dr. Holmes, a well known chest specialist, who had been in private practice in Atlanta, Georgia, since 1922, retired from active practice in July, 1945, and had been living at Atlantic Beach, Florida. He had been a member of the staff of the Atlanta Tuberculosis Association since 1922 and formerly was President of that group. In 1938–9 he served as President of the American College of Chest Physicians. He was also a member of the American Academy of Tuberculosis Physicians, Georgia State Medical Society, Fulton County Medical Society, American Medical Association, Southern Medical Association, National Tuberculosis Association, Southern Tuberculosis Conference, and the Federation of American Sanatoria. He was the author of numerous published articles on chest diseases. Dr. Holmes received his medical degree from the Johns Hopkins University School of Medicine in 1919.

GLENVILLE GIDDINGS, M.D., F.A.C.P.,
Governor for Georgia

DR. PAUL FORREY STOOKEY

Paul Forrey Stookey, M.D., F.A.C.P., died November 25, 1945. Dr. Stookey became a Fellow of the American College of Physicians in 1936.

Dr. Stookey was born in Cedar Rapids, Iowa, September 17, 1888. He received the M.D. degree in 1913 from the Chicago College of Medicine and Surgery and subsequently undertook postgraduate studies at the University of Minnesota and the University of Vienna.

Dr. Stookey was a member of the Jackson County Medical Society, Kansas State Medical Society, Kansas City Southwest Clinical Society, Kansas City Academy of Medicine, Mississippi Valley Dermatological Society, and Southern Medical Association; and was a Fellow of the American Medical Association.

Dr. Stookey held appointment at the University of Kansas School of Medicine as Associate Professor of Contagious Medicine, and at the Kansas City Western Dental College as Professor of Immunology and Head of the Department of Experimental Medicine. He served as Senior Consulting Physician and Director of Services, Isolation Department, Municipal Hospital of Kansas City; and as Attending Physician, at St. Mary's, St. Joseph, and Research Hospitals.

DR. HAROLD EUGENE ROBERTSON

Harold Eugene Robertson, A.B., M.D., F.A.C.P., Rochester, Minn., died March 8, 1946.

Dr. Robertson was born in Waseca, Minn., October 8, 1878. He attended Carleton College and studied medicine at Columbia University and the University of Pennsylvania, receiving the degree of Doctor of Medicine from the latter school in 1905. His postgraduate studies were conducted at the University of Berlin and the University of Freiburg. After appointments as Instructor in Pathology at the Albany Medical College and the Harvard Medical School, Dr. Robertson joined the Faculty of Medicine of the University of Minnesota and rose to the position of Professor of Pathology and Director of the Department of Pathology, Bacteriology, and Public Health. He also served as Professor of Pathology in the University's Graduate School, Mayo Foundation, and as Head of the Section on Pathologic Anatomy of the Mayo Clinic.

Dr. Robertson was a member of Phi Beta Kappa, Sigma Xi, Olmsted County Medical Society, Minnesota State Medical Association, Minnesota Academy of Medicine, Society for Experimental Biology and Medicine, Minnesota Pathologic Society, and Federation of American Societies for Experimental Biology. He was a past President of the American Association of Pathologists and Bacteriologists, and of the International Association of Medical Museums. Dr. Robertson, a Fellow of the American Medical Association and, since 1920, of the American College of Physicians, at one

time held the position of Director of the American Society for the Control of Cancer.

Dr. Robertson served as a Major in the Medical Corps of the American Expeditionary Forces during World War I, and was on inactive duty during World War II.

DR. MAURICE ALEXANDER KUGEL

Maurice Alexander Kugel, A.B., M.D., (Associate), died early in March, 1946, at Miami Beach, Fla.

Dr. Kugel was born in Russia, August 4, 1899, and came to this country at an early age. He attended Harvard College and the Yale University Medical School, graduating from the latter in 1926. His postgraduate work was done in Berlin, Hamburg and Prague. He served on the staffs of the Mt. Sinai and Beth Israel Hospitals, New York, N. Y.

In 1936 Dr. Kugel removed to Miami Beach, Fla., and has since served on the staffs of St. Francis Hospital and the National Children's Cardiac Home, of which he was Medical Director. He was a member of the Dade County Medical Society, Florida State Medical Association, and the American Heart Association, and a Fellow of the American Medical Association. He was also a past President of the Miami Heart Association. Dr. Kugel became an Associate of the American College of Physicians in 1942.

DR. MURRAY BURNES GORDON

Murray Burnes Gordon, M.D., F.A.C.P., of Brooklyn, N. Y., died June 29, 1946. Dr. Gordon was born in Russia, July 4, 1886. He attended the Long Island College Hospital and graduated in 1908 with the degree of Doctor of Medicine. He held an appointment as Professor of Clinical Pediatrics in the Long Island College of Medicine from 1930 until his demise, and as Clinical Professor of Pediatrics in New York Polyclinic Medical School and Hospital from 1937 on. He held hospital appointments as Attending Pediatrician and Endocrinologist at the Israel-Zion Hospital, Brooklyn; Visiting Physician, Kingston Avenue Hospital, Brooklyn; Consulting Pediatrician, Rockaway Beach Hospital and Dispensary and Infants Home, Brooklyn. Dr. Gordon became Chief of the Endocrine Clinic of the Long Island College Hospital in 1923.

Dr. Gordon was a member of the Kings County Medical Society, Brooklyn Pediatric Society, Associated Physicians of Long Island, Medical Association of Greater New York, Medical Association of the State of New York, Association for the Study of Internal Secretions and a Fellow of the American Medical Association. Dr. Gordon was a prolific writer of papers dealing with topics in his chosen field of endocrinology. He was a diplomate of the American Board of Pediatrics. Dr. Gordon became a Fellow of the American College of Physicians in 1919.

DR. MARR BISAILLON

Marr Bisaillon, M.D., F.A.C.P., Portland, Ore., died June 3, 1946 at the age of 63. Dr. Bisaillon was born in 1882 in Minneapolis, Minn. He received his M.D. degree from the University of Oregon Medical School in 1911. He became a member of the faculty of his alma mater and held for many years the position of Assistant Clinical Professor of Medicine. He was Co-medical Director, Portland Open Air Sanatorium; member of the staffs of Multnomah and St. Vincent's Hospitals. Dr. Bisaillon was a member of the North Pacific Society of Internal Medicine, Portland Academy of Medicine, Portland City and County Medical Society and the Oregon State Medical Society. He was a Fellow of the American Medical Association. A diplomate of the American Board of Internal Medicine, Dr. Bisaillon became a Fellow of the American College of Physicians in 1921.

DR. FRED M. SMITH

Fred M. Smith, M.D., F.A.C.P., was born in Yale, Jasper County, Illinois, May 31, 1888. He received his B.S. degree from the University of Chicago in 1913; M.D., Rush Medical College, Chicago, 1914; intern, Presbyterian Hospital, Chicago, 1914–1916; Associate in Medicine, 1918–1920; Instructor in Medicine, 1920–1923 and Assistant Professor of Medicine, 1923–1924, Rush Medical College; Professor and Head, Theory and Practice of Medicine, State University of Iowa, 1924–1946.

Dr. Smith was Assistant Attending Physician, Presbyterian Hospital, Chicago 1918–1924; Attending Physician, Evanston Hospital, 1923–1924. Physician-in-Chief, University Hospital, State University of Iowa, 1924–1946.

Dr. Smith was a member of the Chicago Society of Internal Medicine, Chicago Institute of Medicine, Central Society for Clinical Research, Society of Experimental Biology and Medicine, American Physiological Society, Association of American Physicians and Vice-President of the American Society for Clinical Investigation.

Dr. Smith was a Fellow of the American College of Physicians since 1930 and College Governor for the State of Iowa, 1939–1942; Chairman of Section on Practice of Medicine, American Medical Association; Editor-in-chief, "American Heart Journal"; Diplomate, American Board of Internal Medicine. He wrote the section on diseases of the heart in Musser's "Internal Medicine."

Dr. Smith was fortunate in being associated with Dr. James B. Herrick when the early work on the clinical diagnosis of coronary thrombosis was being done. He showed that experimental myocardial infarction induced in dogs by coronary artery ligation resulted in electrocardiographic patterns similar to those in Herrick's cases. His interest and studies then extended to many other phases of coronary artery disease, the general fields of cardi-

ology and internal medicine. He represented a happy combination of investigator, clinician and teacher. His many friends throughout the country join his family in mourning their great loss.

Five years ago he suffered an attack of the condition to which he devoted much study, coronary thrombosis. Although he curtailed his work somewhat thereafter, he remained actively at work. On February 23, 1946 he had a fatal second attack.

BENJAMIN F. WOLVERTON, M.D., F.A.C.P.,
Governor for Iowa

DR. FRANK MANLY FULLER

Frank Manly Fuller, A.B., M.A., M.D., F.A.C.P., Keokuk, Iowa, died March 19, 1946, at the age of 77. He was born in Keokuk, September 29, 1868. He attended Parsons Academy and Parsons College, Fairfield, Iowa, and graduated in medicine from Keokuk Medical College in 1897. He served on the instructional staff of Keokuk Medical College, 1898–1908; for many years on the staffs of the Graham Protestant Hospital and St. Joseph's Hospital; served as Chairman, Secretary, and member of the Iowa State Board of Medical Examiners; as President and Vice-President of the Federation of State Medical Boards of the United States; as President of the Iowa State Medical Society, of which he was a life member; of the Lee County Medical Society, of the Iowa Clinical Medical Society, of the Southeastern Iowa Medical Society; and of the Des Moines Valley Medical Society. He served during World War I, overseas, as Captain, (M. C.), U. S. A.; served his city as Alderman and as physician to the Board of Health; he was a Fellow of the American College of Physicians since 1920, and was a diplomate of the American Board of Internal Medicine.

Dr. Fuller until his last illness, was an enthusiastic and vigorous student and practitioner of medicine. He was a hard worker in all of the medical organizations of which he was a member, and an eloquent proponent of everything he considered progressive and for the general good. He was much in demand as a consultant in medicine.

His loss will be keenly felt in all the medical organizations in which his face had long been so familiar.

BENJAMIN F. WOLVERTON, M.D., F.A.C.P.,
Governor for Iowa

DR. CHARLES WILSON MILLS

Charles Wilson Mills, A.B., M.D., F.A.C.P., Tucson, Ariz., died September 29, 1945 of coronary occlusion at the age of 66.

Dr. Mills was born at South Williamstown, Mass., September 1, 1879. He attended Williams College and the Johns Hopkins University School of

Medicine, from which he received his M.D. degree in 1908. Choosing tuberculosis as his specialty he had a distinguished career. Following early appointments as Associate Physician, Loomis Sanatorium and Resident Physician, Cragmor Sanatorium, Dr. Mills served as Medical Director, Tucson-Arizona Sanatorium, 1920–21 and of the Tucson Tubercular Charities Hospital, 1921–27. Subsequently he became Associate Medical Director of the Desert Sanatorium and Institute of Research and a member of the staffs of the Southern Methodist and St. Mary's Hospitals.

Dr. Mills was a member and past President of the Pima County Medical Society and a member of the Arizona State Medical Association, National Tuberculosis Association, Southwestern Medical Association and a Fellow of the American Medical Association.

A diplomate of the American Board of Internal Medicine, Dr. Mills became a Fellow of the American College of Physicians in 1929.

DR. TERRANCE CALVIN MOYER

Terrance Calvin Moyer, M.D., F.A.C.P., of Lincoln, Nebraska, died suddenly Sunday, September 8, 1946, following a subacute attack of coronary thrombosis. Dr. Moyer became ill while playing golf at the Lincoln Country Club and died in a hospital a short time later. He was 58 years old.

Dr. Moyer was born in New Berlin, Pennsylvania, March 21, 1888. He was graduated from Union Seminary in New Berlin in 1908, and received his B.A. degree in 1911 and his M.D. degree in 1914 from the University of Nebraska. Dr. Moyer served his internship at Wise Memorial Hospital, Omaha, Nebraska, followed by graduate study at Columbia University. In 1915 he entered practice with his uncle, the late Dr. C. C. Moyer of Lincoln. During World War I he served in the Army Medical Corps at the Base Hospital, Camp Lee, Virginia. He was released from active duty in 1919 with the rank of Captain, and held a Major's commission in the Reserve Corps until 1926. Upon honorable discharge from the Army in 1919, he entered private practice in Lincoln, specializing in internal medicine, his particular interests pointed toward diseases of the lungs. He was a member of the staff of the Bryan Memorial and Lincoln General Hospitals and a lecturer in the school of nursing.

Dr. Moyer was President of the Lancaster County Tuberculosis Association, a Fellow of the American Medical Association, the American College of Chest Physicians, and of the American College of Physicians since 1934; a Diplomate of the American Board of Internal Medicine, member of the American Trudeau Society, the American Heart Association, National Tuberculosis Association, and the Association for the Study of Internal Secretions. He was also a member of the American Legion Lincoln Post Number Three and belonged to the Last Man's Club. He was a Scottish Rite Mason, member of the Shrine, the Royal Order of Jesters and the Lions

Club, and a past president of the Zodiac Club. His fraternities were Sigma Alpha Epsilon and Nu Sigma Nu.

Dr. Moyer was untiring in his professional work, the welfare of his patients always being his uppermost thought. His pleasing and sparkling personality and his wide interests, first in his profession and then in outdoor life, gained for him the love and respect of his confreres, his patients and his friends. He was an enthusiastic fisherman and cameraman, and kept a photographic record of his outdoor activities. He took great pride in his farms and their development, and hoped to retire to one of his farms in Pennsylvania near his birthplace.

Dr. Moyer is survived by his wife, the former Minerva Fuller, and two daughters, Mrs. Claude S. Wilson, Jr., of Boulder, Colorado, and Jo Ann, who resides at the family home.

Dr. Moyer's passing is a great loss not only to the medical profession but to his patients and friends as well.

J. D. McCarthy, M.D., F.A.C.P.,
Governor for Nebraska